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P A R T I C I P A N T S

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S. Gerald Sandler, M.D.
Mark Skinner, J.D.
Wing-Yen Wong, M.D.

Non-voting Government Representatives

Jay Epstein, M.D.
Harvey Klein, M.D.
James S. Bowman III, M.D.
Matthew Kuehnert, M.D.
CDR Mike Libby

C O N T E N T S

TOPIC III: CURRENT AND EMERGING INFECTIOUS PATHOGENS; SHARPENING OUR APPROACH FOR THE 21ST CENTURY TO REDUCE THE RISK OF TRANSFUSION TRANSMITTED DISEASES

C O N T E N T S (Cont.)

P R O C E E D I N G S

DR. HOLMBERG: I'd like to call the meeting to order, and have the roll call. Judy Angelbeck?

[No response.]

DR. HOLMBERG: Celso Bianco?

DR. BIANCO: Here.

DR. HOLMBERG: Mark Brecher?

DR. BRECHER: Here.

DR. HOLMBERG: Paul Haas?

MR. HAAS: Here.

DR. HOLMBERG: Andrew Heaton?

DR. HEATON: Here.

DR. HOLMBERG: Chris Healey? And, Chris, would you like to make an announcement?

MR. HEALEY: Thank you. I don't know how you knew that, Jerry, but yes.

I just wanted to let my fellow Committee members know that this will be my last meeting. It's been an honor to serve on the Committee for the last two years as a representative of the Plasma Protein Therapeutics Association, but I'm

delighted to let you know that I'm leaving the organization and I'm going to be joining the Grifols organization as their Vice President for Public Affairs, so I'm sure our paths will continue to pass, and look forward to the chance to work with you all in the future. It's been an honor to serve on the Committee. Hopefully I've made a few contributions, and I'm sure that the very capable people at PPTA will be nominating somebody to complete out the term.

So thank you very much.

DR. HOLMBERG: Thank you, Chris. Thank you for your service.

Jeanne Linden is absent.

Karen Shoos Lipton?

MS. LIPTON: Here.

DR. HOLMBERG: Gargi Pahuja is absent.

Dr. Sandler?

DR. SANDLER: Here.

DR. HOLMBERG: Dr. Sayers is absent.

Mr. Skinner?

MR. SKINNER: Present.

DR. HOLMBERG: Mr. Walsh is absent.

Dr. Wong?

DR. WONG: Present.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Dr. Epstein?

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Klein?

DR. KLEIN: Here.

DR. HOLMBERG: Dr. Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Commander Libby?

CDR LIBBY: Here.

DR. HOLMBERG: And Dr. Gomperts?

DR. GOMPERTS: Here.

DR. HOLMBERG: Okay. I'll turn it over to you, Dr. Brecher.

DR. BRECHER: Thank you, Jerry.

We're going to be changing topics now. I just wanted to say also that we are going to be on time today, if not early. I'm aware that several members have early flights, so we're going to be

really adhering to the timetable if not getting ahead of it.

So we're going to go to the current and emerging infectious pathogens; sharpening our approach for the 21st century to reduce the risk of transfusion transmitted disease. We are going to have a report of the Emerging Transfusion Transmitted Disease Subcommittee. However, Jeanne Linden was not able to make it to the meeting, and Jay Epstein has graciously agreed to give a brief presentation regarding that committee.

DR. EPSTEIN: Thanks very much, Mark.

The Subcommittee that was established to address transfusion transmitted diseases, as noted, was chaired by Jeanne Linden, and the members included myself, Mark Skinner, Matt Kuehnert, Jerry Holmberg, Andy Heaton, in addition to--and Karen Lipton.

We met several times by teleconference, and began I guess logically by looking at specific agents of concern. Initially we were focused on emerging infectious diseases, but as we began to

discuss the issues that presented themselves, we came around to thinking that the more useful approach for this Advisory Committee would be to look at the public health system as a whole and to ask how we could begin to identify gaps and help establish priorities in dealing with the known and emerging transfusion transmissible diseases.

So it was on that basis that we developed the format for today's agenda which will more or less follow this logic: First to review our current knowledge of the existing threats and the potential for transfusion transmission; then to look at the existing frameworks, what are the strategies being used by the various Federal agencies; and then through a series of case studies looking at specific etiological agents to try to bring forward an assessment where the strengths and weaknesses have been in approaching these different threats. Then we hope that that will serve as the backdrop for a discussion of gaps and priorities for the system as a whole.

So that's a little bit brief, but on a

moment's notice, Mark, I think that does explain how we got to where we are.

DR. BRECHER: That was very good. Thank you, Jay.

Now for our next wrinkle. Our next speaker could not be physically present and will be presenting his lecture from a telephone. This is Mark Smolinski, who's Vice President for Biological Programs at NTI. Dr. Smolinski was a Senior Program Officer at the Institute of Medicine of National Academies of Science, and study director for the report "Microbial Threats to Health Emergence, Detection and Response." He's a physician and expert in medical epidemiology and public health. He has served in various senior positions in the Federal, state and local government, including senior advisor to the U.S. Assistant Secretary for Health and Surgeon General, and an Epidemic Intelligence Officer for the U.S. Center for Disease Control and Prevention.

DR. SMOLINSKI: [Via telephone.] Good morning.

DR. BRECHER: Could you turn that up, please? Go ahead, Mark.

DR. SMOLINSKI: Thank you. I'm sorry I couldn't be there in person. I broke both my feet while on vacation in California and was ordered by the orthopedic surgeon yesterday when I saw him to give it more rest, so I'm trying to be the good patient and follow doctor's orders.

I've identified, numbered them, so on Slide No. 1 there, I just will take a moment to tell you about NTI for those of you who may not know about our organization. This is a public charity that was started with funds from Ted Turner. He co-chairs the initiative with former Senator Sam Nunn, and basically our mission is to reduce the threat from chemical, nuclear and biological weapons.

Slide No. 2. [Inaudible.]

DR. BRECHER: Okay. We've got it, Mark, but we're having a little difficulty getting your volume up.

DR. SMOLINSKI: Oh, okay. No. 2 is

[inaudible] weapons of mass destruction. Biological weapons are the greatest concern to me. It's one that scares me to death. And this was Colin Powell when he was, at that time, giving a talk as the Joint Chief of Staff at the Armed Services Committee in 1993.

Slide No. 3. Let's remember those charged with protecting us from attack have to succeed 100 percent of the time. To inflict devastation on a massive scale the terrorists only have to succeed once, and we know they're trying every day. That was Dr. Condoleezza Rice as the National Secretary Adviser in 2003.

And finally, No. 4, the anthrax incidents and two unambiguous [inaudible] vulnerable to bioterrorism and we are now prepared. That was John Marburger in 2003.

Slide No. 5. The Microbial Threats to Health Report. Basically at the time that we were working on this report we were following up on the 1993 report, which was a landmark report at the time. But this is our philosophy. And the report

was basically that the best defense against any microbial threat is a robust public health system in its science capacity, practice, and through its collaborations with clinical and veterinary medicine, academia, industry and other public and private partners.

And that's the philosophy we also follow at the Nuclear Threat Initiative, although we do work on weapons of mass destruction within the biological program for which I'm the Vice President. We really are focusing on improving the global capacity for early detection and surveillance of all infectious diseases. So we're building a lot of global surveillance systems. We're currently working on one in the Middle East that is connecting Israel, Jordan, the Palestine Authority and Egypt, and our philosophy is that our funds are going to help with real daily threat in infectious diseases with hopefully building the infrastructure that would be necessary should an intentional release of an agent be used in the future.

So Slide No. 6 is basically the definition that the Committee came forward through, which is the spectrum of all microbial threats. And basically those are newly-recognized pathogens, of which we've had numerous in the last few decades. A new geographical spread. Maybe it was a disease that we knew about before, but now is seen in areas where it was not endemic in the past, and that would be an example such as what's now a virus when it came to the United States. Resurgence of endemic infections, and of course, we still have great concerns about plagues such as HIV in new areas of the world. Malaria and TB are still leading causes of death around the world. Antimicrobial resistant infections; the Committee spent a lot of time dealing with that issue. The [inaudible] chronic disease which [inaudible] something where a lot of research has shown [inaudible] chronic diseases, the cancers. And lastly, the intentional use of biological agents, so our approach was to really look at bioterrorism as really just the far end of the spectrum of all

microbial threats.

So in Slide No. 7, it shows leading infectious causes of death worldwide. Infectious diseases till remain the top cause of death in most developing countries. There was a lot of concern about how to get the United States citizens and policymakers to really deal with infectious diseases in the United States.

And No. 8 is a slide that shows despite progress and announcements in the early 1950s, '60s by the then Surgeon General Stewart, who said that we have conquered infectious diseases and we need to move to chronic infection. This slide basically shows that even when you account for the diseases and deaths that are due to the HIV virus, that we still seeing a rise in infectious disease deaths in the United States.

Slide No. 9 is a graphic that you've probably all seen many times and we tried to update, but basically shows that we have seen numerous new infectious diseases identified across the globe in the last two decades, and I think the

figure that Tony Fauci uses at NIH is that we've seen two new infectious diseases per year for the last two decades, and these are diseases that were not known in the past.

So Slide No. 10 was really the pinnacle of the 1993 Emerging Infectious Report from the IOM that identified the factors in emergence. Of course those were the human demographics in behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and then the breakdown of public health measures.

And so the challenge in doing a report that follows such a well-received report was identifying the factors that we've seen in the last decade that the Committee did not really focus on back in 1993 because that report was specifically looking at emerging infectious diseases in the United States, and of course, times have changed dramatically in the last decade, and now infectious diseases are really global burdens because we have no borders for microbes.

In Slide No. 11 the Committee identified seven additional facts in emergence which were really based on the global aspect of emerging infectious diseases. And those were: the changes in human susceptibility to infection, with more people who have chronic disease, the older population, people with HIV/AIDS, people on long term immunosuppressants for cancer and other diseases; really the recognized science regarding the changing weather and climate and the impact that that has had on emerging infections; changing ecosystems, really we've come a long way in understanding the implications of man living in various environments and the impact on the natural infectious diseases in those areas; poverty and social inequality which is really a huge problem in the persistence of emerging infectious diseases in developing countries; following on that would war and famine, the lack of political will in dealing with a lot of these issues; and then finally, the last factor in emergence is the intent to harm or the human aspect to emerging infections.

So the next series of slides, Slide No. 12, these are just to show some data on some of these factors. No. 12 is the human population explosion which is pretty self-explanatory, to see where that would have an impact on the emergence of infectious diseases, not only with humans being in closer proximity to each other, but also just in all the social factors that relate to emergence of infectious diseases.

No. 13 shows the world urbanization trends, and of course we see more emerging infection when we have overcrowding and poor sanitation in urban areas, and that this urbanization trend has been in all aspects of different economic situations and different parts of the world, not just in developing countries but in developed countries as well.

No. 14 shows the trends in travel, and these are the international tourist arrivals, and this shows that in all parts of the globe we've had dramatic increases in persons coming from other areas of the world to visit those particular areas.

No. 15 shows the international agricultural trade, and we have dramatic increases in the sharing of fruits and vegetables, meats and other products, dairy products and even live animals, and these have a dramatic impact on emerging infectious diseases and spreading diseases to areas where they were not previously seen.

Slide No. 16 is a nice slide to show the impact on vector control. This is the distribution of [inaudible] that just die in America. If you look in the 1930s, that was when we were at the height of the problems with malaria and other diseases in this particular vector. In 1970, the middle picture, shows the height of our vector control program, and then with all the problems with the potential impact on the environment and other issues revolving around DDT use and other pesticides. We can see in 2003 we're back to where we were in the 1930s, with the distribution of the [inaudible] that just die in the Americas alone.

Slide No. 17, I was on the original investigation team of hantavirus in 1993 when that

was newly discovered in America, and as you can see here in this slide, in the last decade new world hantaviruses have been identified in all parts of the Americas along with the rodent vector that carries that. So when we identify new emerging infectious diseases oftentimes it's probably a disease that may have been around for a while, and with our newer technologies and ability to identify diseases, we can discover that these were actually around in other parts of the world as well.

So to put that all together, Slide No. 18 was a graphic that the Committee developed as a model for really thinking about all of these factors and how they impact on emerging infections. And the center of the box is really meant to sort of represent the proverbial black box, and with the black being what we don't know and the white being understanding these factors, so of course we would want this box to go from black to all white. But it's impacted by the main interaction between the microbe and the human shown in the solid boxes in the center, and then all of the factors in

emergence, those 13 that we identified--and of course we expect that people will identify other factors in the future--are really within the four realms of the physical environmental factors, the ecological factors, the genetic and biological factors of both the microbe and the human, and then probably the largest group of factors fall into the social, political and economic factors.

So we hope that this model--we know that the report has been used in a lot of schools as a textbook on emerging infection, and this is sort of a teaching tool to really examine some of the factors, and it has also been used, we have been told, by various organizations and so forth, focusing on specific diseases where they can fit in their various factors into the model.

So Slide No. 19, which is really the critical slide here for your group, looking at our IOM recommendation, and this is just a summary line of each of these, and I'll just spend a couple minutes on each to tell you if there's a highlight.

The first recommendation was really the

need to improve global surveillance and response, and this was really a call for within the policymakers of the United States to really realize that our investments in the CDC and NIH and other Federal institutions, FDA and so forth, you know, we really need to focus on looking at the international implications of disease surveillance and response, and that our resources within the United States are validly spent overseas in looking at issues with emerging infectious diseases, because with all the factors with global trade and travel and so forth, the diseases that are happening in other parts of the world are really as much of a concern to ours, and I think that was clearly highlighted with the irony that the day we released the report was the day that the news about the SARS outbreak in South Asia was identified, and that was a clear example of an emerging infectious disease due to all those factors we're talking about became a global threat within a matter of months. So this was a really important call for America to wake up and really try to improve the

surveillance capacity and response around the world for emerging infectious diseases and also for monitoring diseases that are endemic to many areas as well.

The second was to rebuild the domestic public health capacity, the public health system, as you know, in this country has really been neglected for several decades, and the Committee was calling for a robust public health system as really being our first line in responding to emerging microbial threats, so there's a lot of rhetoric and dialogue about the need to rebuild this public health capacity here in the United States.

Third was to improve disease reporting. There was a call once again to educate and train health care providers to really report infectious diseases, not only the reportable diseases but any unusual clusters of disease as most emerging infectious diseases, including the hantavirus, Legionnaire's disease and others, were really reported by student clinicians recognizing a new

syndrome was occurring.

Fourth was exploring innovative systems of surveillance, and the Committee really had called at that time for pilot testing, syndromic surveillance, which was all the rage at the time, and emphasizing that this is not a proven strategy and that we should explore it in the pilot project as a research tool, but cautioned against wide use of syndromic surveillance until it's determined that it was actually an effective tool, and I think that the verdict is still out on that. To this date we really have not had a syndromic surveillance system that is shown to be cost effective.

The next recommendation was developing and using diagnostics. There was a real call for this, the need for improved diagnostics. We still don't have quick diagnostics for influenza virus, which is critical when we have the flu season, and really screening those who would benefit from antiviral therapy, and really the need for diagnostics for many emerging microbial threats.

The next one was to educate and train the workforce. This was on all the issues, emerging microbial threats and the need to really improve our training in infectious diseases in general.

The next one was really a call that we were in a critical stage in developing vaccines and antimicrobials. There is not one single new class of antimicrobials in development. There are new drugs in the pipeline that are just different versions of former classes, and that seems is at a critical stage. As you know, we've had shortages in numerous vaccines for childhood diseases, and we've always had problems with influenza in the last few years, and we had very different methods suggested for possibly alleviating this problem, but we are at a critical stage for vaccine and antimicrobials.

We went a bold step in banning the use of antimicrobials in animals for growth promotion, which was a call for an issue that we were really behind in the United States. Other countries have already banned the use, but we have not taken that

step here in the United States, and the Committee went so far to actually call for a ban here in the United States. Again, with that one slide I showed about vector control, we really need to invest in improving vector disease control in the United States.

And then finally, the last recommendation was develop a comprehensive research agenda. It was a call for moving from investigator driven grant request and funding for specific disease projects and other research projects to really getting the Federal Government to focus on developing an agenda of what needs to be done in order to understand all of the factors that emerge and to develop a comprehensive research agenda so to fund research that would actually answer very needed questions rather than just haphazardly just refunding research as it's requested by individual investigators, and that's been something that NIH has actually responded to and has been working on, trying to develop a comprehensive research agenda.

So that's just a quick overview of the

report and the recommendations. I think there's just a final slide that's a cartoon. And I know that this was a very pressed schedule for everything that you're trying to get [inaudible], and I'd be happy to answer any questions that you might have about the report or any of the recommendations and so forth that we put forward in that.

DR. BRECHER: Questions from the Committee?

DR. BOWMAN: [Off microphone, inaudible.]

DR. SMOLINSKI: Yes, yes, we did. In the first recommendation we talk about the role of WHO, and in supporting WHO in really playing the lead role for global infectious diseases. I can speak as an organization. NTI, we have invested heavily in the last two years with WHO. Some of the things that we have done because we personally felt--Peggy Hamburg and I, who worked on the report, are the sole staff in the biological program at NTI, so it was a great opportunity to move from having worked on this report to an organization that actually

gave out money. And so one of the first things we did was develop the Global Response Fund at WHO because one of the concerns was when there's a global outbreak, depending on what country it's in, trying to get the money together to put a team together and move to that area has been an issue. So we developed of a half a million dollars for WHO to respond to any outbreak in the world, and then worry about getting the money to replenish that fund from a revolving fund from donor countries. So when we instituted that three years ago, it has been used over 20 times to immediately respond to outbreaks including SARS, and it has been replenished every time. So they still have the original half million dollars in that fund.

We're also concerned in the area of bioterrorism that many countries are turning to the World Health Organization for questions on determining whether they are prepared for not only bioterrorism events but for the issues on global emerging infectious diseases. So we have heavily invested in the Department of Communicable Diseases

at WHO, and specifically in their Preparedness for Deliberate Epidemic, and Senator Nunn has actually called for the Secretary General to make this a priority at WHO in the United Nations, and the reason we were investing in this is because we felt this is a critical issue and we were trying to leverage other funders. And since that has happened they have identified this as one of their priorities for the new millennium.

We've also helped WHO develop their Global Public Health Intelligence Network, which was formulated by Health Canada, which is how WHO currently identifies over half of the outbreaks around the world, and it was only done in English by scanning media sources and other electronic data to identify rumors of disease which were then validated by staff at WHO, and so NTI provided the resources that as of last November the chief in network is now available in all languages of the United Nations.

So as an organization we are really investing heavily in WHO because we believe that

they do serve as the natural role for dealing with global emerging infectious diseases, and have just not had the adequate resources and funding, and so we have yet to see in the new millennium, while it has been identified as a priority, whether they will have the capacity to take this on as a global issue. But it is an important organization and the Committee did talk about WHO quite a bit in the report.

DR. HOLMBERG: Celso, I'll relay your question.

DR. BIANCO: [Off microphone, inaudible.]

DR. HOLMBERG: The question from Dr. Bianco is do you see the blood donor as a surveillance worldwide?

DR. SMOLINSKI: You mean using testing of the donor blood supply for surveillance of infectious diseases?

DR. HOLMBERG: Yes.

DR. SMOLINSKI: I think that I guess it comes down to the real ethical issues of doing sero surveillance unbeknownst to the person who's

donating the blood, and I don't know what kind of--that's not something that I studied in those respects, but certainly it has helped with the emerging infectious diseases such as hepatitis C and other diseases that have been identified, and I believe people understand are routinely tested in the blood supply. So, yes. I mean I think that there's--it's a great potential value for doing some sort of surveillance, but it's just a matter of the ethical issues about what are you detecting and are you giving this information back to the person who's donated the blood, and all the things that surround that.

But I think if we could work those issues out it's a great source. I know even when we were studying the hantavirus in the United States in 1993, we were able to discover that hantavirus was actually in that area of the world because there were studies that was done where blood was saved and stored from up to 10 years earlier for a maternal child breast feeding study in the area of the world that was affected, and it was determined

through that that the hantavirus was identified as having been around 10 years earlier, so there is certainly value in the wealth of information that's contained in the blood supply, so it's just a matter of trying to work out the ethical issues about what is right to test and how do we relay that information back if at all to the people who have donated the blood.

DR. HOLMBERG: There's a question from Dr. Gomperts.

DR. GOMPERTS: [Off microphone, inaudible.]

DR. HOLMBERG: I'll see if I can capture that. Over the last--in your report, over the last couple decades, there's been at least two emerging pathogens appearing per decade. What kind of analysis did you do worldwide on that to see any kind of epidemiological events? Is that pretty close?

DR. SMOLINSKI: I think I get the gist of it. That data is basically just--and as a correct statistic--is just based on those diseases that we

know about. One of the things that we're finding out as we are developing these surveillance systems around the world, for instance, I just got back from a month in India where we are developing a surveillance system that is going to work in South Asia region, and I'm getting ready in two weeks to go to Pakistan. Pakistan has no surveillance system. A few particular systems where they've had funding for polio and measles, but nothing at all for emerging infectious and other diseases, which is pretty typical of most of the other areas of the world, especially in the Middle East.

So, no, the data that we have is only based on those areas where something has been identified gratuitously, but certainly it's probably much higher than that if we were to have the capacity to even detect emerging infectious diseases, but most areas of the world are really struggling with the diseases that they know about of which the surveillance systems are so poor so to really have the capacity to identify new and emerging infectious diseases is virtually nil in

most parts of the world. So I think we'll see those numbers go up dramatically as we build these systems and have people looking for unusual clutches of diseases and sharing their specimens with places like the Center for Disease Control in the United States, and now we're have a European Center for Disease Control and other research institutions which will be able to potentially identify new diseases because most people who die around the world from infectious diseases are probably not even identified with the cause [inaudible], or it's written off as one of the diseases that are endemic in that area.

So, no, we have very poor surveillance for emerging infections in other areas of the world, and like I say, those two per year is just based on those that somehow we were able to identify through the work of the World Health Organization investigating large outbreaks of something that was identified as a public health crisis, or again, just gratuitously that it happened to be in an area of the world where they had the capacity. So, no,

that's certainly a very conservative estimate on the true emerging infectious diseases.

DR. HOLMBERG: Dr. Gomperts has a follow-up.

DR. GOMPERTS: [Off microphone, inaudible.]

DR. HOLMBERG: I don't know if you heard that.

DR. SMOLINSKI: No.

DR. HOLMBERG: Over the last decade, just looking at the 20 emerging agents that have been identified, has there been analysis on, for instance, mutational changes, vectors, what kind of analysis has been done on the top 20?

DR. SMOLINSKI: There have been specific studies done on some of the larger outbreaks if the resources were available through the World Health Organization or within the country where they occurred. For instance, the outbreak--just to give you one example, the outbreak of dengue in India, which was I believe in 1994 or '95, and there was a lot of sort of environmental work done because it

was felt that that was due to the heavy flooding that was done in the area, and the change in the populations of the rats in that part of the world. And as I was in India meeting with various organizations, there now is concern that that data has not held up and that they are seriously investigating whether that was an intentional release of plague in that part of the world.

So that's been one area where they have investigated and the hypotheses that were initially reported may have not proved out, so they are looking at a potential bioterrorism events in that part of the world.

Certainly the West Nile virus here in the United States had a lot of people working on that, and it was felt that somehow it got over here in the United States, whether the vector itself is transported in a wheel well of an airline or whether an infected passenger came over here, because certainly the mosquito populations within the United States were able to transmit that vector, and so it wasn't like we had to have a huge

new vector infect the United States. Certainly the mosquito population we had here was capable of transmitting that virus, which is a big concern.

But when it comes to vector-borne diseases and zoonotic diseases, of which 75 percent of all emerging infectious diseases that are zoonoses, and that's including the vector-borne--one of the concerns that the Committee has expressed and is highlighted in the workforces, we have very few new scientists going into these areas, especially in entomology and vector control, and you know, we have had more people going into veterinary sciences, but the concern is, do we even have the capacity here in the United States to adequately study how these diseases are transmitted or the factors that are involved, and certainly we don't have that globally when it comes to zoonotic diseases of which most of these are involved.

So again, I think we have a lack of resources to truly invest in what the factors are that cause these emerging infectious diseases around the world, both financially and in

workforce. So, no, there's probably very few of those diseases that have been investigated in the way that I think you are suggesting, of really looking very closely at. Most of them have been responding to the actual public health threat in reducing the transmission, and unfortunately, in most of the parts of the world where these emerging infectious diseases have resulted in these large outbreaks, there just is not the capacity to do the studies that we're talking about doing.

And hopefully, as we are investing in--you know, even in the funds I the United States for bioterrorism and looking at some of these Class A, Class B agents, of which many of these emerging infectious disease are in other parts of the world endemic, even though they're listed as bioterrorism agents in the United States, that we will be spending more resources in really understanding these diseases in other parts of the world, which, you know, from my perspective is a plus for public health because we can help to really solve some of the endemic issues in other parts of the world

while we're preparing for a potential use of that agent intentionally within the United States.

So that's a long answer to your question, but I really just think the lack of resources have really prevented understanding these emerging infectious diseases completely. Even with hantavirus in the United States, which is on that list, the amount of resources that have been devoted to that disease by the CDC is very little when you compare it to some of the other diseases, but they have done longitudinal studies using GIS and other new tools to monitor the population density and to look at the food supply for the rodents and stuff in that area, and were successful in predicting the second wave of hantavirus that occurred several years later based on some of those studies that they did on the hypothesis that it was due to heavy rainfall, increase in food supply for the rodents, and then naturally an increase in the rodent density. And so the hypothesis from the 1993 outbreak led to some investments in those studies in improving by prediction that it would

follow the next wave of environmental issues that mimicked what happened in 1993, and indeed, we had a second really epidemic proportion of hantavirus in the United States.

So there is an example where they did invest some resources in and were able to determine that that is how that emerging infectious disease spread. But certainly we have more resources here in the United States for those things than they do in most of the other countries.

DR. HOLMBERG: Mark, if I could ask a question concerning your statement or the findings from the IOM regarding strengthening our public health infrastructure, you know, you just made a comment that we in the United States have a substantial amount of resources. However, what specifically was the IOM referring to there? The reason I bring this up is that we heard this comment yesterday also in some of our discussions, so I would appreciate just a short answer.

DR. SMOLINSKI: sure. I think our number one concern was the training and the education of

the current public health workforce. So in other words, if you go into most local health departments, of which I've had the privilege of working in several, most of the people who are working in the epidemiology departments and in the infectious disease departments do not have public health training. These are jobs that are very hard to fill because one of the key factors is the salaries are abysmal, and they have to fill these jobs with people who have education but do not have training in public health to run some of these positions.

So we have a real call for increasing the funding for training people in public health and really trying to make the salaries in public health comparable to some of the other jobs that are pulling people who do have masters in public health, or at least have gone through some public health training, for being pulled up by private industry and other areas that are looking for that kind of training as well. So we really need to educate and train our current workforce through

continuing the amount of [inaudible] and other venues, and at the same time we have to increase the number of people who are in the pipeline coming through public health because of the concern that we're never going to fill that void if we don't invest in getting people properly educated in the area of public health now.

And schools of public health have been struggling around the country and we need to invest more resources in those issues. And public health is sort of one of those things that, you know, it's a victim of its own success. You know, it's hard to really emphasize the role that public health plays, because when it's successful in preventing diseases in a community and is doing a good job in disease control, people see it as an invisible force that they don't really understand.

But I think things changed a lot within even the general public after the anthrax outbreak, and in seeing how public health played a critical role in that area, and certainly in the SARS outbreak as well. So I think in general the public

education has gone up about the importance of public health and we're trying to translate that into excitement on Capitol Hill about the real need for public health. Certainly, whenever we do hearings about bioterrorism and other emerging infections, that's our number one message to Capitol Hill and to other policymakers is that we have to invest in public health in this country because these are the people who we need to fill the jobs that are going to serve as our first line of defense. So increasing education and training of the current workforce and trying to get more people into the channel of public health and other allied health professions that work on these issues is something that we really have to try to support.

DR. BRECHER: Okay. We have to move on, I'm afraid.

DR. HOLMBERG: Mark, we're going to have to call it quits here. Our schedule is really tight. I'll give you a call tomorrow. Thank you.

DR. BRECHER: Our next speaker is Roger Dodd. Roger is the Vice President of Research for

American Red Cross Holland Labs. He'll provide an overview of the current blood borne infectious threats to the blood supply.

DR. DODD: Thank you very much, Mark. I'm pleased to be here.

I was asked to give you background on the factual aspects of emerging newly recognized transfusion transmissible infectious agents, and I will also spend a little bit of time on bioterrorism agents inasmuch as I know much about them. And the errors are my own. I've tried to use the same format for each agent so it will be a little bit repetitive.

First I want to speak about parasitic agents. Then we'll talk a little bit about bacterial agents, viral agents, TSEs, and finally bioterrorism. This is just a schematic to introduce the topic of malaria. Malaria is a classic re-emergent infection. It is reappearing in areas from which it was once eliminated, perhaps due to climate change, although that is a controversial issue. So malaria's endemic in the

shaded areas on the top left here, basically the tropical areas of the world, globally, but also occurs elsewhere, and one of the things that we need to be concerned about epidemiologically essentially inexplicable malaria which has been occurring all over the United States for many years. And if you can see the dots on the bottom diagram, this is where such unexplained cases have occurred in the United States over many years, actually mimicking the original distribution of malaria in the country. Of course it's a mosquito borne infection, and it's an intra-erythrocytic parasite.

There are four species of Plasmodium with somewhat varying properties that are responsible for malaria throughout the world, and as you well know, infection can lead both to acute and chronic infection and disease from the asymptomatic to the fatal. Some of these agents like malaria indeed have very long-term infections, although mostly we think of this as being an acute problem in the United States.

I've shown you the transmitting mosquito and the distribution, and globally there are some three to five hundred million cases annually, mostly in sub-Saharan Africa, and 1.5 to 2.7 million deaths which more or less encompass the figure you previously heard. In the United States, although it varies quite a lot from year to year, currently there are about 1,000 imported cases annually, so these are individuals who have traveled in and returned from malarious areas and come down with the disease here in the U.S., and these are explicable, unlike the points that I showed you in the previous slide.

Globally this is probably--and this is a matter of opinion--but I would say probably the most frequently transfusion transmitted infectious disease. The agent itself can survive in stored cellular products and essentially, certainly in the United States, all blood recipients are susceptible to malaria transmitted by transfusion. Of course, the disease is usually worse in the older and the immunocompromised.

In general we see two to four transfusion cases annually in the United States and these can be tracked to a variety of causes. Sometimes it's ineffective use of our primary preventative measure, which is questioning donors about their travel history. Occasionally it's a result of long-term infection that these measures really don't deal with. We actually--I think this last figure is probably not true in the Red Cross program, which represents about half of the blood in the United States. Currently we're deferring about 40,000 donors a year on the basis of their travel history, and this deferral requirement is currently quite strict, and involves essentially any country where malaria is endemic even for a short visitation, and even, for example, stepping ashore off a cruise ship. In fact, it's my recollection that most of the transfusion transmitted malaria cases of recent years have actually been tracked back to Africa, West Africa, and have related to longer term than expected infections and people who have come from Africa.

So that's malaria. I apologize, I'm going to rush through all of these, but this is what I had to do.

We have in the United States, and actually globally, but of most concern I think in the United States as transfusionists is another infra-erythrocytic parasite, Babesia. Babesia microti is the most common agent found in the United States, and it's endemic in animal and human populations in the coastal northeastern states and in the upper midwest. Other piroplasms have been identified from Missouri, Washington and California.

This disease is endemic by and large in deer, but also affects mice, and is transmitted by the deer tick which is actually a very small tick, and people rarely recognize that they've been bitten by the Ixodes deer tick.

It generates an acute disease with up to six months worth of subclinical infectivity, which I think is longer than had previously been supposed. It is a treatable disease, but has been fatal for selected patients, particularly blood

recipients. It is of particular concern to individuals who have been splenectomized, older individuals, which is obviously older than I am, and those who are immunocompromised.

I told you it's transmitted by ticks, and its distribution in the United States. This is not a reportable disease, but if you look at seroprevalence rates from donors and others, in general they'll run up to 1-1/2 percent in endemic areas in the United States.

Transfusion transmission of Babesia is being recognized in the U.S., and one case has been reported from Japan. The parasite survives in erythrocyte-containing components and some transfusion transmitted cases have actually been tracked to platelets, platelets which probably were contaminated with red cells.

The outcomes, as I told you, are worse in the aged, the splenectomized and the immunocompromised, and we now know that there have been more than 50 transfusion cases to date, and the demonstrable risk in studies that have been

performed by Rich Cable--and David Leiby will be speaking to you later today--is as high as 1 per 1,000 transfusions in the highest incidence areas of Connecticut, that is, coastal Connecticut. And this has been defined by actual observation of transmissions rather than by extrapolation from seroprevalence rates.

The risk is increasing in the United States primarily because the geographic spread of the agent, its hosts and vectors, and the tendency of the suburbanites to want to go back to nature and live in amongst the deer. Even in the suburbs here of Washington, D.C. I'm shooing deer out of the yard almost every night, when they eat my bird feed in the winter and they eat my plants in the summer.

Really with respect to transfusion safety there is no available effective intervention. There are efforts made towards donor population management, in other words, there are attempts made not to collect blood from individuals in high risk areas, and we used to say in the high season, but

given the relatively prolonged asymptomatic infectious period, this isn't as easy as we had thought.

Hospital vigilance and recognition of disease is important, along with recipient treatment. And there is a potential for testing of donors. Whether that testing would be by serologic or by nucleic acid methods is a question that remains to be answered, although it now looks as though there might be more help than we had previously thought for serologic methods.

Chagas disease is not endemic amongst human populations in North America, well, North America beyond Mexico, although in fact both the parasite and affected vectors do exist in the United States, and there was a fairly well-reported case of a young baby bitten in its crib in Tennessee I think, Tennessee or Kentucky, who developed Chagas disease in the United States. So the organism is actually between the 40th parallels north and south, but human conditions in South and Central America permit a much more effective

interaction between the humans and the insect vector which can live in substandard housing, comes out at night and bites people. This is a free Trypanosome, which you can probably see in the bottom right here.

So it's a protozoan parasite. It's free in blood, although it has a tropism particularly for smooth and cardiac muscle. It generates both acute disease which is generally relatively trivial, but much more importantly in most cases, perhaps 40 percent of more, a chronic and essentially lifelong infection which can be asymptomatic but can frequently lead to fatal disease, most often unexpected arrhythmias and heart problems, although there are also intestinal problems associated with invasion of the smooth muscle.

It is a zoonosis that affects many, many mammalian species, but is transmitted by the bite, although not directly by the bite, of the triatomine bugs, one of which I showed you. They're ugly looking things. Celso can tell you

that.

I told you where the agents are in the Southern cone in particular and Central and parts of Mexico, Central America, parts of Mexico. There may be 19 to 20 million infected individuals. The incidence in the endemic areas is declining because of relatively effective programs of vector control have been implemented, but vector control is based really on dealing with houses and households, and the bug can live free in the wild, so there will always be some baseline level.

Even 15 or 20 years ago there were at least 100,000 Chagas-infected individuals in the U.S. as a result of population movements. These were legal population movements. And continuing influx of people from South and Central America is keeping this up, and not incidentally, as more focus is put on hispanic donors, we are seeing some increase in transfusion transmitted Chagas.

In South America the perceived wisdom is that susceptible patients have a 12 to 50 percent chance of being infected if they receive

seropositive blood. I don't know how true this really is. This figure's been around for a long time, but I would point out that sero surveys have generated among donors seroprevalence rates of up to as high as 50 percent in parts of Bolivia. Again, studies by David Leiby have shown that for seropositive individuals in the U.S., somewhere around about 60 percent of the them are parasitemic as demonstrated by PCR.

The organism survives well in stored components. Most infections in the U.S. appear to be derived from platelet components, but whole blood is also a source of infection, particularly in South America.

The agent causes severe disease in immunocompromised patients, and there are at least seven reported cases of transmission of T. cruzi through transfusion in North America. But the estimated seroprevalence rate nationwide, based on point estimates around the country and figures relating to immigration would be somewhere between 1 in 40 to 1 in 25,000.

The risk is increasing in the U.S. population, as I mentioned, and at this stage there is no effective intervention available. It's been clearly shown that questioning about origin is nonspecific and other questions about potential exposures are not sensitive and certainly not specific. Were an antibody test to be available, it would certainly be an effective preventative measure for preventing transfusion transmission. In our own studies almost every seropositive individual had been many years in this country and had obviously been infected early in life in an endemic area.

Leishmania, don't have too much to say about that, but it is the subject of both current and past concern with respect to transfusion transmission. The concern is primarily related to troop and civilian deployment in Iraq and Afghanistan where this infection is widespread. It's transmitted by sandflies. And there have been a few historical examples of blood borne transmission, although if you look closely, most of

these don't relate to frank transfusion activities, but rather transfer of blood. There are no known current cases of transfusion transmitted Leishmania. And the current intervention, which in a sense is more of a theoretical threat and a theoretical response is to defer returnees from the Middle East conflict areas currently for one year.

I think there was some discussion as to whether we were going to talk about bacterial from the perspective of bacterial contamination, and I thought the consensus was that we weren't, but I have a couple of slides here anyway. This is a topic that's very familiar to this Committee and clearly one of the big residual problems in the United States has been outgrowth of bacteria in components for transfusion. This can generate acute to fatal disease in recipients, and the contaminants most often found, skin contaminants, environmental contaminants, or actual donor bacteremia, and the last of these probably causes the most severe outcomes, as they tend to be rapidly growing gram negatives.

The occurrence is generalized, and the frequency of this event depends very much on the measures that are used with perhaps 1 to 1,500 platelets with reactive cultures or blood cultures. Actually our own data right now say that only about 1 in 6,000 aphoresis platelets are definitively contaminated as based on aerobic culture at 24 hours after collection. The overall figure is still 1 in 1,500 because there's lots of contaminants and false positives around.

Careful studies, for example, in Johns Hopkins, suggest that you can get a reaction which is due to bacterial contamination in about 1 in 20,000 platelets transfused, and Matt Kuehnert's BaCon studies suggest about 1 in 100,000 transfusions result in sepsis on the basis of reporting from hospitals. So you pays your money, you takes your choice, but the potential threat is certainly quite high, although it's being well-managed at this time. The frequency of outcomes is greater among platelets because they're stored at room temperature; then red cells and then very

little from plasma.

All recipients clearly are susceptible. Out comes can be worse in immunocompromised and generally fragile patients. I believe--although we don't have definitive data, but Red Cross data on reporting suggests that the risk has been falling as a result of--now in association with the intervention, I don't want to make any public claims about blood safety here, Jay. And an intervention has been essentially mandated by both the AABB and College of American Pathologists, which have a standard that require limitation and detection of bacteria in platelets for transfusion.

A specific bacterium, anaplasma phagocytophilum, the agent of human granulocytic ehrlichiosis, is one of these agents that travels around in ticks along with Lyme disease and Babesiosis. Again, it's common in the Northeast, the upper Midwest, and is, as I said, transmitted by ticks. Only one suspect transfusion case has been reported from St. Paul some years ago. It was not definitive, but it was certainly very

suspicious. This is an organism that, obviously by its name, hangs around in white cells, but there is no definitive intervention at this time.

I would say in passing that asking donors whether they've been bitten by a tick proves not to be very efficacious because, I think in general, those people who know they've been bitten by a tick will remove the tick during the latent period or the grace period and not being infected. Those people who do not know that they are bitten are the ones that get infected.

Prevalence for this organism, seroprevalence, is quite high, up to 3.5 percent in endemic areas. So one that we need to keep our eyes on I think.

As far as other bacteria, just running through very quickly, the agent of Lyme disease, this is certainly the most widespread tick borne disease in the United States, but there have been no definitive reports of transfusion cases. There's an interesting case of a co-infected donor reported by Rich Cable in Connecticut, and the

recipients of blood from that donor developed Babesiosis, but not Lyme disease.

Bartonella is blood borne, is of concern. It's a relatively mysterious organism and I know of no transfusion transmitted cases.

Rickettsiae and anaplasma was among the Rickettsiae group in general, are in issue, and there was a CDC workshop some years ago that discussed things like Rocky Mountain Spotted Fever where there are actually no transfusion cases.

Orientia has in vitro capability for transmission, but this has not been proven. And chlamydia, another classic long-term intracellular bacterium, has been looked at, but we have no cases of transfusion transmission. Still worth examination.

Briefly, we know all about West Nile virus. Just wanted to point out that the global distribution as of year 2000 was the blue section for the JE Group, and those of you with acute eyes will notice the Queens outbreak is noted on the U.S., where the brown color actually represents St.

Louis encephalitis. And the two maps on the right show the human by county distribution last year for West Nile virus infections among humans and the overall activity, so it's reached every state in fact except the state of Washington and Hawaii and Alaska, very rapid spread of an externally introduced organism.

It's an envelope RNA virus of the flavivirus group. It causes acute infection with asymptomatic to fatal disease. Its transmitted by mosquitoes but the normal cycle is usually from infected birds, although many other vertebrates have been shown to be infected. Normally present in Southern Europe, Africa, the Middle East to India, and it arrived in the U.S. in 1999, and endemic essentially throughout the continent by 2004. In 2002 and 2003, which were banner years in the U.S., probably about 400,000 individuals were actually infected. That's quite a blast.

Transfusion transmission was essentially unknown, is rare to absent outside the United States. We now know that the virus itself survives

in all stored components, and that most recipients are susceptible to infection, although the majority do not show definitive disease. In 2002 there were 23 documented transmissions of West Nile virus by transfusion, but the risk profile as of today is unknown, and if you talk to the vector borne infection folks at CDC, they are only--the word "declining" really reflects the fact that they will decline to offer any estimate of where this epidemic has gone.

In 2003 after the implementation of nucleic acid testing of all donations, about 1-1/2 to every 10,000 blood donors were RNA positive with significantly higher rates in the higher incidence areas. At one point we measured a point prevalence of 1 in 47 in parts of Nebraska in 2003. It ended up being about 1 in 100. So the infection rate can be extremely high. The unusual thing about this from the perspective of how we usually think about transfusion transmitted infections is the fact that it's an acute infection with a relatively short viremic period, and up to this point we've been

most focused on those organisms that have prolonged asymptomatic viremia. So obviously if you get enough infection, an acute infection can be and is transfusion transmissible.

HHV-8, human herpes virus 8, is the most recently described human herpes virus, although it's been around human populations for a long, long time, and we have to be careful to differentiate newly appearing infections from newly recognized infections. An envelope DNA virus, it generates chronic persistent infection and is almost certainly the responsible agent for Kaposi's sarcoma, both the classic, that is, the African version, and that which is HIV associated. And to some extent this virus travels with HIV, and from that perspective is an emerging infection in the United States.

It's transmitted person to person, certainly by the sexual route, and most commonly by male to male sex. There are some publications that suggest that in common with some other herpes viruses, it's transmissible through saliva and is

almost certainly transmitted by organ transplant. It probably has a global distribution, Africa, parts of Southern Europe, and is quite common among men who have sex with men.

The seroprevalence rate is very much test dependent, and one of the difficulties here is that there's no real gold standard test. Different tests for different viral components or viruses collected, developed by different methods, have widely differing seroprevalence rates. But frequencies among blood donors of up to 2.4 percent in this country have been reported, although this does not correlate at all well with the frequency of viral DNA amongst cells from these individuals.

In terms of HHV-8 and transfusion--and you'll hear more about this later today--in my opinion there's no direct evidence of transmission by transfusion, but there's certainly rather suggestive epidemiologic evidence, and there are data indicating a higher frequency of HHV-8 infections among transfused populations, for example, in Africa, and the frequency increases

with the frequency of transfusion. There's also some data that suggested that at least some injection drug users, female injection drug users had a higher seroprevalence for HHV-8.

The jury is out on this one, but the predominance of evidence in my mind suggests that we need to consider it as a highly likely transmissible agent by transfusion. The blood environment was concerned some years ago by the recognition of DNA for HHV-8 in a seropositive donation, but we know nothing about recipient susceptibility or a risk profile for donors, and there is no clear intervention, although men who have had sex with men and many people who have come from Africa are already excluded from donation. There would be a potential for development of an antibody test, but I think that's got a long way to go at this stage. The whole diagnostic scenario for herpes viruses is pretty tricky, in my mind.

SARS we spoke about. A new coronavirus, perhaps transmitted by us biting animals, rather than the other way around, this is the civet cat

which was thought to be a potential source of infection in Guangdong province in China. As a result of air transportation, it spread rapidly over many parts of the world and created a great deal of alarm, despondency, although the human epidemic, as shown in the last slide, really just peaked and essentially has disappeared. Those of us who travel a lot will recognize that there's still a lot of concern, and we pass by thermal imaging cameras entering and leaving Hong Kong and parts of Canada, so there continues to be alarm and surveillance here.

As we all know, this creates an acute infection, an asymptomatic to fatal disease very rapidly transmitted person to person presumably by the aerosol and its thought by the fecal-oral routes, and was likely a zoonosis transmitted from animals to humans by unusual practices. Originated, as I said, in the People's Republic of China and was rapidly globalized, and about 8,500 cases were reported worldwide in the single epidemic in 2003. The U.S. caseload--actually I'm

just being lazy here--but was somewhat unclear because we had a somewhat different case definition from WHO, but was probably around 60 cases.

No transfusion cases of SARS were reported, but because of its rapid onset, its obvious fatal course and general concern, there was a lot of worry about potential transfusion transmission. This was not helped by the fact that fairly early on the virus itself was found in the kidney of a deceased patient and subsequently in the blood of symptomatic patients by nucleic acid testing. This is unusual for a purely respiratory virus, but certainly added fuel to the fire of concern about transfusion transmission. I guess I'd say the risk is currently apparently absent, but I think we do not know how well the food chain source is being managed, and I think it's a solitary example of the explosive emergence of a zoonosis.

Intervention for transfusion transmission was by exclusion of patients, travelers and case contacts, and this was implemented fairly rapidly,

but again, generated another difficult set of questions.

Other viruses that we need to think about. Dengue has already been mentioned. It's emerging or re-emerging. It's nipping at the borders of the United States in South Texas. There was an outbreak in Hawaii. It's all over South America. It's present in Puerto Rico. One case of transfusion transmitted dengue virus was reported from Hong Kong a couple of years ago, and a little earlier than that there was a potential case that resulted from a marrow transplant in Puerto Rico. Again, its behavior is very much like that of West Nile virus. There was an imported epidemic in the holiday areas around in Australia a couple of years ago that also created a reaction and concern there.

Simian foamy virus we've heard about. There's certainly animal transmissibility of this retrovirus, and the FDA has expressed concern about its potential transmission by transfusion. The concern was not echoed by their Advisory Committee, but it's out there. To date, however, we believe

this is a nonpathogenic virus.

Then there was a group of circoviruses, TTV/SENV, and another flavivirus, all of which were isolated in association with patients who had hepatitis, but turn out probably not to be evident causes of hepatitis. They're certainly transmissible. We don't know if they're pathogenic, and no action has been taken. And actually I would add as an aside that you'll probably realize as you go through the day that there has been no consistent pattern of action with respect to emerging infections, and that in some cases the same degree and level of evidence has led to very different outcomes with respect to taking action to preserve the safety of the blood supply.

Very briefly, variant CJD is a transmissible spongiform encephalopathy, a prion disease, a degenerative fatal disease with a lengthy incubation period, and almost undoubtedly results from consumption of tissue from bovine spongiform encephalopathy infected cattle. Most cases of the human disease have occurred in or been

associated with the United Kingdom, about 152 cases, and 6 to 10 others have occurred in Europe. Cases have been reported from Hong Kong, from the United States and from Canada, single cases, but all were thought to be due to exposure in the United Kingdom, and no endogenous case of this disease has occurred in the United States.

Concern about transfusion transmission has been high despite the infrequent occurrence of the disease itself. Animal model data suggests that the infectious prions, both of this and other TSEs, are likely to be present in all blood components, although the titers of the infectious agent are very low in plasma products.

The susceptibility of recipients to development of disease as a result of exposure to blood carrying the agent is unknown, but there have been two said to be suspect, but I think very likely true cases of transmission of variant CJD by transfusion in the United Kingdom. One led to frank disease. It resulted six years after receipt of a blood unit from an individual who himself died

of variant CJD three years after giving the blood. The second case of transmission of the agent resulted in surveillance studies on a patient who died of unrelated disease, but had received blood from an individual who subsequently developed variant CJD. This patient had the infectious or the putatively infectious prion, the pathologic prion detected in the spleen in a cervical lymph node. One of the side issues here is that this particular patient was heterozygous for methionine at codon 129, which is different from all the other cases of variant CJD recognized to date, all of which occurred in individuals who were homozygous. This has led to suspicion that there might be a second wave of infection waiting in the wings.

The risk for vCJD itself appears to be declining in the United Kingdom based on data from the U.K. TSE Surveillance Program, but there is now some concern that we may see a second wave of infection if heterozygotes are ultimately susceptible.

The intervention in the United States is

based of course upon management of the food chain, but primarily for transfusion on eliciting a travel history from blood donors.

I was asked to say a few words about agents of bioterrorism, at least the Class A or top tier agents as defined by CDC, and these are anthrax and botulism, although what we're really talking about is the use of botulinum toxin, and because the toxin per se is not transmissible, I'm not going to speak to that. Plague, smallpox, tularemia, and perhaps the viral hemorrhagic fevers, and I think I probably have about one slide on each of these.

Anthrax is from Bacillus anthracis, which will probably be transmitted or distributed in the form of spores, and the inhalation route is the most likely to be used.

There's a seven- to 40-day incubation period, although potentially longer, particularly based on some animal work. However, there is no person-to-person transmission, but there is potential for bacteremia so that the blood safety

would be potentially compromised in the event of an anthrax attack, either as a result of external contamination of blood, blood packs and so on, or actual or fear of donor infectivity.

I think that many of us really got quite a jolt when the anthrax attacks in the United States had occurred because I think we were all set up to figure out how to deal with a very widespread distribution of anthrax spores, in which case the objective would be just to close down the blood supply in the affected region and support from outside. But, in fact, with a handful of cases and no knowledge of how big the exposure was, we really had quite a lot of difficulty in dealing with anthrax. So I think we have to be flexible and recognize that there may be more than one presentation for these kinds of attacks.

Plague is another bacterial infection. *Yersinia pestis* is the agent of concern, and, again, in terms of a bioterrorism attack, the inhalation route is most likely. And obviously the idea is that you get a lot of incapacitating fatal

disease, so that most of the time we're going to be dealing with symptomatic disease.

The incubation period for inhalation plague is a short one to six days, but pneumonic plague may be transmitted person to person by exhalation, by droplets, by aerosol route. The mortality is high and is rapid after onset if treatment is not initiated within 24 hours. Again, bacteremia clearly occurs and blood safety could be compromised, although, again, I remind you there's a very short incubation period. But part of the problem will be managing fear and concern.

Smallpox, variola major, is an enveloped DNA virus, again, transmitted by the inhalation route, with a 12- to 14-day incubation period, with person-to-person transmission from symptomatic cases, either by droplets or by contaminated fomites, bed linen and so on. And we all remember that contaminated blankets brought the end of some native populations in earlier days of biological warfare.

The population currently is thought to be

highly susceptible because of the absence of or fading of efficacy of smallpox vaccination, and the patient is certainly viremic during the symptomatic phase. Blood safety would clearly be compromised, and with its relatively long incubation period, I think that this would be extremely difficult to manage.

Tularemia, *Francisella tularensis*, again, this is an endemic infection particularly of rodents in California and elsewhere. But for a BW attack, the inhalation route again would be most likely. The incubation period is usually three to five days, but with a range of one to 14, and the outcome in this case is a pleuropneumonitis.

There is, in fact, no person-to-person transmission, but there would clearly be bacteremia, and this is an agent that sits in leukocytes and macrophages, and this would be a problem in early infection. So, again, from the face level, blood safety would be compromised.

Viral hemorrhagic fevers--and we're talking about a fairly wide range of agents here,

some of the really scary ones, Ebola, Lassa, Marburg, and so on. Again, inhalation route would be most likely to be used. The incubation period is 3 to 15 days, and there would be and it's well known that there is person-to-person transmission b aerosol and direct blood contact. And we've all read books like "The Hot Zone." We've all known about the problems associated with Ebola. There is, of course, a very extensive viremia here, and blood safety would be definitively compromised. And the other aspect for viral hemorrhagic fevers is that their management may, in fact, need extensive transfusion if the patient is to survive. So we not only have a loss of availability of blood, but we also will potential have an increased need for it.

So my overview--and I thank you for your patience--is that there are numerous emerging and newly recognized infections with the potential for transfusion transmission. It involves all classes of agents. There is no common pathogenesis or transmission route or infectious period or clear

risk factor. And right now, for most of the ones that I have spoken to, there is really a clear absence of effective interventions. And I might say in the context of this meeting there does not seem to be a systematic approach to dealing with these.

Thank you.

DR. BRECHER: Thank you, Roger. Maybe you could take a question or two. Jerry?

DR. SANDLER: Dr. Dodd, I'd like to pick up on your last bullet and ask a question about pathogen inactivation. There's a popular notion that if the pathogen inactivation processes that are under development could eliminate the problems of toxicity, you could retire, that the level of concentration of the pathogens in an asymptomatic person walking in to donate blood are such that they should be effective, and your last bullet, that there are no effective interventions, leaving out prion diseases, that this might not be a problem. I know it can only be an opinion, but can you give us--because your opinion would be very

informed.

DR. DODD: Thank you, Jerry. I think it's a good point, and I apologize for omitting discussion of it.

I would perhaps take a little issue with your comment that the level of viremia or, actually, agent-emia, if you like, in an asymptomatic infection may be such that the current available methods or currently to be available methods would always work. Again, it's my opinion, and it's very hard to tease this out because most of the data that you see from these procedures shows maxed out inactivation. But, in fact, we know, for example, that the B19 virus can accumulate to 10^{12}, 10^{13} particles per mL. That's an extreme case. But even something like hepatitis C virus, potentially we're up around 10^{6} per mL in an asymptomatic phase of infection. And I think that one would have to--really for complete assurance in these cases, one would really have to use the procedures in association with testing.

I think for some of the other agents that

have been discussed here, particularly the parasitic agents, there's a very good chance that it would be effective. It's an open question, for example, as to whether it would have been completely effective with respect to West Nile, although data have been developed that suggest that this is the case, that it would indeed have been effective.

So I think I would answer your question partially, yes, I think in many cases we could expect that this would have a very significant impact, and even if it didn't prevent infection, the levels would be relatively low. And it might be unlikely that there would be major disease. But I don't think it's the guaranteed panacea. I don't think it's evident that this would prevent everything. And my current belief is that in the United States as of today I will be retired before this comes in, but that's maybe a statement of my intent rather than of the science.

DR. BRECHER: We'll go down the row here, Karen, Matt, and then Harvey.

MS. LIPTON: Roger, I'm going to ask you a question that I actually wanted to address to Dr. Smolinski, but I didn't think he would really have a perspective, and it really deals with the role of hemovigilance in--do you see that there is any need for the creation of a hemovigilance system in the U.S. as a vehicle for, you know, tracking these diseases, preventing--or, you know, hopefully preventing transfusion-transmitted further spread.

DR. DODD: Karen, I think you're right, and over the years many people have discussed ways of almost predicting outcomes or looking for viruses without even looking for disease. And if you talk to the experts in the field, they say you always need a disease before you can really take action here.

I think your point is well taken. I think that the deficiency in my mind of any hemovigilance system to date has been that the reporting phase of it has been either explicitly or implicitly voluntary, and that's really, I think, where the weakness of hemovigilance lies.

But, on the other hand, I believe that the majority of transfusion-transmitted infections certainly in the United States have been recognized as transmissible as a result of clinical vigilance. And I think that probably the most recent and clear example of this has been West Nile virus. And it was clinical observation, it was recognition, along with a heightened concern, that really led to the recognition that this was going on.

So in a sense, I believe that there is a process of hemovigilance going on, but I also think that we need to have the awareness to work through this and to make sure that training and recognition procedures are out there. Whether we could double or treble the efficacy of this by a formal hemovigilance is something for you guys to think about. But clearly it's important.

DR. KUEHNERT: I think your comments about putting the clinician in the pathway is very, very important because they're going to be in the pathway whether we put them there or not. They're the ones who transfuse.

But I wanted to ask you a question about--I was interested to see that the sort of concern pyramid was sort of inverted in your presentation, where usually we have viruses as the largest bulk of the talk and then bacteria and then parasitics might get half of a slide. And you've inverted that, and I think that warrants some further discussion. And I wondered, adding also prions to that list, that pyramid, how you would design a process to prioritize these threats.

DR. DODD: Well, I think that's really a very difficult question. I actually prioritized them by the amount of nucleic acid rather than by threat. And I think that's what Ed was trying to get at in his questioning. And I think that what you're asking, Matt, is: What should we be looking for? What has history told us? What's the next bad actor to pop out of the box?

I think it's very hard to say, but I have to say that I don't think that we're going to get explosive outbreaks of parasitic disease. So I think that perhaps you shouldn't see my

presentation as any more than what I said, nucleic acid content.

DR. KUEHNERT: But the thing--sorry to interrupt, but I'm not actually asking that, how to look on the horizon for new pathogens, but how actually to prioritize even with some of the pathogens we already know about, which may be actually more of a threat than those that are unknown.

DR. DODD: I think that's the difficulty, because I usually look at two axes of prioritization. The first is the public health threat, which is basically how much disease, how serious the disease, how readily you can establish treatment or intervention. But then there's an entirely different threat, which is one axis that really doesn't interact very well, and that is what sort of public, political concern is generated by these agents. So that to take perhaps, oh, I don't know, a couple of examples: HIV everybody would agree was very high, both on the public health and public concern axis. Variant CJD is probably much

higher on the public concern axis than it is anywhere on the threat axis. But sometimes it's public concern that drives it more than anything else.

I don't know where you'd put, for example, HHV-8 on that, but I do think that you need an open and explicit thought. The other issues are really explosiveness of what's going on. I mean, SARS was just a fantastic example of an explosive outbreak that really had to be dealt with well ahead of there being any information.

West Nile, we actually had a fair amount of time to think about it. We had publications in August of 2002 saying, well, it might be transmissible to this extent. I mean, we sort of needled Lyle Peterson until he did it. And two weeks later, we had the first cases coming out. So timeliness is yet another axis.

I think that you might be able to systematize the structure, but everything is still going to have to be case by case.

DR. KLEIN: I'm glad to hear that when it

comes to genomes, size doesn't count, Roger.

[Laughter.]

DR. KLEIN: But if we look at history, it's very likely that the next agent is going to be a virus, and probably one that has a long silent period, such as HIV had. And yet the ones we're concerned about are the explosive ones like SARS, and I quite agree with your point. I hope the committee will consider that, that we don't have a consistent approach to these agents. And so my question is: We've seen SARS. What data do we have about the presence of the agent in blood prior to the onset of the clinical disease? Or what data do we have now about silent cases, if there are any? And have we looked appropriately?

DR. DODD: Yeah and no. This was something certainly that the transfusion field was asking for, but obviously it turned out to be very, very difficult. I think that CDC--and perhaps you know more about this than I do, Matt--was very much aware of these issues and did try to do some caregiver studies and some sequential studies on

contact. But the very nature of this is that, you know, the fire has burnt out by the time you find the can of gasoline, I guess.

I think that there have been seroprevalent studies that have been performed post facto, and it really turns out, particularly in the areas of high frequency of disease, it was quite an alarming amount of clear seroprevalence. So this is not an infection that invariably led to disease.

Whether or not those in apparent cases or the early cases were viremic, I don't know. Matt, did anything ever come of those studies that we were asking for?

DR. KUEHNERT: Just in ten seconds or less, I think that that summarizes it well. I think we're concerned about an asymptomatic viremic period just before the onset of symptoms, but that's very difficult to capture unless you have a cohort of people that you know are at risk and then do serial blood draws. We do have those protocols in place, and we've worked very hard to put in that to measure by PCR in blood samples, which often

gets sort of left off the map when looking at, you know, the disease pathogenesis.

The other concern that I have is how long the viremia remains, and there's some more data now on that that's somewhat reassuring. But it's certainly much longer than we first suspected. But I think it's a matter of, you know, concern and all we can do is try to put the studies in place to be able to look at it were there to be a resurgence in the future.

DR. BRECHER: We're going to move forward to try to keep us on time. So we're going to take a ten-minute break. We're going to hold discussion until later this morning. Ten minutes.

[Recess.]

DR. BRECHER: We're going to begin again. We're going to start looking at the system process approach to current and emerging infections, and Karen Shoos Lipton, who is the CEO of the American Association of Blood Banks and a member of this committee, will present an overview of the blood organizations' approach to current and emerging

infectious pathogens.

MS. LIPTON: Thank you. This morning actually I'm speaking on behalf of the three blood organizations, so I'm really not an AABB representative up here but someone who has been nominated to tell you about the different--it's not up there on the screen yet, right?--nominated to tell you about the different processes we have in place in the blood organizations.

To that end, I'll speak about AABB, but if you have specific questions about the American Red Cross approach or America's Blood Centers, we have Dr. Bianco here from America's Blood Centers, and I don't know if Roger is still in the audience but--there he is. I'm sure he can help us out.

From the AABB perspective, I would say that when we talk about infectious disease, the committee that has the primary responsibility for this is the Transfusion-Transmitted Diseases Committee. It really is truly what we would call a standing committee within the organization.

The AABB committee structure is relatively

formal, I would say, compared to other organizations, and so each of our committees has ongoing charges that are changed every year, transmitted to the committee, and they actually have some deliverables every year. Generically, I would say the TTD Committee has these continuing charges. They are to monitor existing and emergent issues. They are to develop proposed position statements, make recommendations to the AABB Board and actually other AABB committees on discrete issues. I think most importantly this committee includes liaisons from America's Blood Centers, American Red Cross, Centers for Disease Control, FDA, and CAP. We periodically add other liaisons as we think it's needed.

A new sort of process that's been developing over the past several years that's proved to be very helpful for us are interorganizational task forces. These are really single-issue entities. We convene them and then after they've completed their work, we dismiss them with thanks. We always say that in the

organization. They're convened to address scientific and operational issues associated with specific problems. They develop information and recommendations to the community, and they include representatives from interested organizations. So by that I mean we will invite an organization to participate. It is up to that organization to designate their own representative.

We do provide fairly significant staff support, or I should say we provide Kay Gregory, and those of you who have worked with her know how wonderful she is at bringing these groups together.

Our AABB committees and what we call our internal task forces are also very important to this process. Most critical to infectious disease issues is our Blood Banks and Transfusion Services Standards Committee. Marianne Silva presented yesterday, and she's in the audience, and she is currently Chair of this sub-unit. There is an overall standards program unit, and actually Dr. Harvey Klein is Chair of the entire standards program unit because the AABB sets standards in a

number of different areas.

The Blood Banks and Transfusion Services sub-unit is responsible for developing appropriate standards or requirements related to specific issues. So if something comes out of an infectious disease issue and we want it to be a requirement, we send it on to that committee. This includes liaisons from a number of different organizations--ACOG, again, the blood organizations, FDA, CDC--and it also includes the State of California because the State of California has actually adopted AABB standards as law.

Our communication bulletins, we really picked two types that we focus on. AABB has something called association bulletins, and it is really what we call the highest-level communication vehicle in our organization with a mind-boggling review process. The purpose of it is to advise members on AABB policy and guidances, to provide information updates. Sometimes it's simply on emerging issues. We also use it to communicate interim standards, that is, those standards that

we're putting in place outside of the normal course of events. And the association bulletins are reviewed annually for their relevance and published, republished.

AABB Pulse Points is really just a rapid communication vehicle. The difficulty with the Pulse Points is it's really only for subscribers and not everyone is a subscriber. So when we're getting something out, we tend to do it through an association bulletin and then announcing it to people in a weekly report. But we are, I would say, more limited in our ability to get out massive amounts of information if it has to be done overnight.

Again, one of the other communication vehicles are the standards that are published every 18 months. They are published requirements for accreditation. They are distributed to all AABB institutional members, and they are also, of course, available for purchase.

America's Blood Centers has really two different or several different processes for

dealing with infectious disease threats. The first is infectious diseases that are not considered to be an emergency, and they use primarily their staff and their Scientific, Medical, and Technical--they call it their SMT--Department to monitor events, and they distribute this information to the ABC officers, to the SMT Committee, which is the standing committee within America's Blood Centers, SMT and quality forums, and to the CEOs of member centers, and the CEOs are then responsible for disseminating the information to those in a need-to-know within the blood centers.

The committees are set up, I think, periodically--you can ask Celso specifically about them, but they are set to review issues, to set priorities for the organization, to propose ABC comment positions and actions, and to organize conference calls to discuss potential threats. I will note in the last hemolysis issue that actually ABC had organized a teleconference for its members on hemolysis, and I think that's a very useful vehicle, and we've actually--we tend to rely--when

I say rely, we've done teleconferences, too, but it's very helpful when the different organizations do things that allow other organizations inside to participate. Committee recommendations are developed by the SMT staff and distributed to members for comment.

When they have an actual position, they get a final document that defines ABC's position, and it's produced for presentation by liaisons to AABB committees because ABC has a liaison on, I believe, just about every AABB committee that exists, and, of course, at official meetings like this. Liaisons are responsible for coordinating activities with the AABB task forces, and as new information becomes available, the same process occurs.

When they get to infectious diseases that are considered an emergency, it's a little bit faster and I guess more truncated process. The SMT staff develop a proposed policy statement in-house, and they submit it to the officers for input. They are capable of developing a position within 24 to

48 hours, and the liaisons are responsible for coordinating actions with AABB task forces that may be relevant to the issue.

A preliminary position is submitted for review by ABC committees and forums as well as the entire ABC membership, and then finally, the final position is developed and revised using the same process.

American Red Cross has a slightly different structure, being a single-licensed organization. They, of course, participate with FDA, CDC, and industry work groups through the medical office and Holland Laboratory representatives. When they have urgent or acute threats to the blood supply, they're managed internally through development of dedicated task forces that are put together, depending upon the specific issue. They can include medical, scientific, operational, and regulatory staff.

When we talk about prospective active surveillance, that's really conducted primarily through the Holland Lab, and their approaches

include literature review, lab investigation, seroprevalence studies, and review by expert or blue-ribbon panels. They are in the process of establishing a permanent standing Medical Scientific Advisory Committee of experts outside the American Red Cross. And anything that's a new test implementation is managed through the Scientific Support Office of the--they call them the NTRLs, National Testing and Reference Laboratories.

The Red Cross describes their overall approach as being coordination, staff communication, and partnership with government agencies.

I'd just like to make a final comment, and that is that it was interesting, we all have somewhat similar processes, but I think we don't have formal processes really in place. What is remarkable is because we are a small community, how fast information travels. And I don't think we've worried in some cases about having a formal process because it's worked so effectively. But I think it

has made all of us think about how we're linked to each other and hopefully we'll have some productive conversations here about not only how to link the blood organizations but then probably most important to link into formally with FDA and with Centers for Disease Control.

So if you have questions about AABB, you can address them to me; if you have questions about ABC, to Dr. Bianco; and to Dr. Dodd for Red Cross.

DR. BRECHER: We have a few questions. Matt?

DR. KUEHNERT: Thanks for the presentation. I just had a question about how we can better enhance communication between the blood community and public health, and I sort of mean beyond CDC. We certainly have very good communication with our public health partners, state and local health departments. But how do you think we could better enhance direct communication between these two communities?

MS. LIPTON: I think that's a very good question, and just so all of you know, when the

most recent association bulletin came out, for those of you who have seen it, there was quite an extensive discussion really about the public health role. And there's always a little pushback because I think that the blood centers are very interested in communicating information. I also think they're very reluctant to become themselves responsible for the public health issues that come up. And so there's always a little bit of tension.

I think that what we're really talking about is an education process. You and I spoke yesterday, Matt, about I think that most blood centers are fairly good about understanding when a viral threat is reportable, but in everyone's mind, bacteria doesn't quite fit into that. And so our point in laying out all the reportable bacteremia was to make sure that people understood that, yes, bacteria can be a reportable disease.

So I think it's probably more education than anything. It really does, though, have to happen, as you know, because it's a state and local issue, at the blood center and at the hospital

level and not as much at the top level of the organizations.

Maybe, Roger, did you have a comment?

DR. DODD: I'd just comment, Matt, that there has been--it faded away and it's coming back again--a very strong relationship with what used to be called the Association of State and Territorial Public Health Lab Directors. I know it's got a new name now. (?) , but it doesn't anymore. And I think actually this should be enhanced and brought back to the fore.

It's interesting that the blood environment was actually the first to deal on a large scale with issues like HIV testing, and we actually inserted a lot of--or tried to insert a lot of good sense into what they were doing, too. So I would encourage, perhaps through the established associations, further development of these kinds of interactions.

DR. KUEHNERT: What I would suggest is actually consider speaking with CSTE--that's the main organization now--about having a liaison at,

you know, some of these levels. We've tried to get them--I mean, there's the flip side, too. Sometimes they're confused about what the public health implications are concerning some of these issues, and so they need education also. So it's a two-way street, and I think they're eager to learn.

MS. LIPTON: I certainly think including them on the interorganizational task force on an issue-by-issue basis is important. And certainly if they wanted to have a liaison to TTD, that would not be a problem.

DR. BRECHER: Jay, last question.

DR. EPSTEIN: Karen, my question is: To what extent do you feel that the blood organizations are contributing proactively toward priority setting, especially with regard to a research agenda for blood safety and availability?

MS. LIPTON: Well, actually one of the charges that I didn't show from our TTD Committee is to annually come up with a list of priorities of issues that we think are important. Now, we also have another committee within the AABB that's the

Clinical Transfusion Medicine Committee, and they identify really more clinical priorities. And at the end, the board takes both of those and puts those together to decide really in terms of resources and trying to put together a plan of how the association can respond to things, what we're going to address.

So we have a fairly formal process to do that. You and I have talked about making sure that we share that agenda with the FDA so that you don't get blindsided on some issues. And I think we're well on the way to doing that. But that really is an ongoing process where we are trying to communicate that. And then we actually do send those research priorities which are vetted through our scientific section, we send those off to NHLBI and make some specific requests for funding for research initiatives.

DR. HOLMBERG: Okay. We're going to move on. Our next speaker is Mary Gustafson. She is the director of worldwide regulatory policy for the Plasma Protein Therapeutics Association, and she's

going to provide an overview from the plasma organizations' systematic process approach to current and emerging infectious pathogens.

MS. GUSTAFSON: Thank you, Jerry, and thank you, members of the committee.

As mentioned over and over again yesterday, plasma therapies, even within therapeutic categories, are unique. They employ different manufacturing processes and different pathogen clearance steps. In light of these differences, the ultimate responsibility for safety of each product lies with the manufacturer. But having said that, there are definite commonalities, and safety issues common to members are addressed by the association.

PPTA depends on its Pathogen Safety Steering Committee to provide leadership in issues of pathogen safety. The Pathogen Safety Steering Committee is a global committee. Our companies are global and therapies are marketed worldwide. The steering committee is comprised of scientific

experts from around the world. It's a science-driven committee with members from primarily the research and development areas within the different companies. It's managed by Dr. Ilka Van Hogan (ph) from our European office, and it's currently chaired by Dr. Thomas Kreil of Baxter BioScience.

The charter of the Pathogen Safety Steering Committee includes as its key element identify and prioritize key safety issues, and we just had a discussion between Matt and Roger Dodd and with Karen that this is a very, very important area because there are different axes of concern, and particularly when dealing globally, and also there's the issue of resources and what you can tackle within a certain period of time.

I might say that the members of the Pathogen Steering Committee already have an extensive time commitment. It's probably our most active committee, and any of the members, besides their day jobs, commit to between four and six face-to-face meetings per year, numerous telephone calls, developing position papers, reviewing

regulatory documents. So it's a very, very active

committee.

The committee monitors and assesses and comments on emerging pathogens, supports liaison activities with authorities from standard-setting bodies and regulatory agencies on scientific issues, and initiates and monitors issue-specific task forces, similar to what Karen mentioned, in terms of a task force to address a specific issue and then, with thanks, go away. However, in the area of pathogen safety, most of our task forces are pretty well continuing.

I also might mention that while the Pathogen Safety Steering Committee has the focus of the association activities related to pathogen safety, the association has other groups that interact on issues of safety, and these include regional regulatory committees and committees that establish our voluntary standards. The outcomes and activities and concerns of all of our efforts are communicated by association publications.

There's a weekly leadership briefing that's electronic. There's the Source magazine.

There's our PPTA website--the address of that is in the very right-hand corner, www.pptaglobal.org--where we try to maintain transparency of our activities. There's the patient notification system and, when needed, specific letters that are sent.

Some of the issues that we've dealt with in recent times from pathogen safety include parvovirus B19. Work was done by the Pathogen Safety Steering Committee and our standard-setting committee that resulted in setting a voluntary industry standard for viral-loaded manufacturing pools and the position that testing should be considered as final product and process test as opposed to donor screening.

The association also acted very quickly in the face of West Nile virus to demonstrate the efficacy of our current clearance steps in removing virus, focus studies with model virus and the relevant virus. These studies helped in the determination that donor testing is not needed to ensure product safety for our fractionated

products.

Our industry has also been very active in research on transmissible spongiform encephalopathy. Studies have been performed to demonstrate prion clearance by our steps in the manufacturing processes. And, in addition, the association has undertaken a study, which is ongoing, to demonstrate the value of equipment and surface cleaning solutions in prion clearance.

One of the PPTA initiatives that fits well within today's agenda is what we call the Emerging Infectious Disease Roundtable. As mentioned, the plasma therapies industry is global, but regulatory bodies are regional, and this results in differences in response to emerging infectious diseases and differences in decisions about donor testing and management and final product testing and management. These differences are counterproductive for manufacturers of therapies that are worldwide and obviously must be confusing and frustrating to patient groups.

To help with this problem, PPTA conceived

the idea of initiating a roundtable to provide a venue for global regulators, consumers, industry scientists, and experts in bioethics, risk management, and print media to begin dialogue to improve communications related to decisionmaking in the face of emerging threats. Two of you at the table participated in our first roundtable--Jay Epstein and Mark Skinner--which was held in March of last year in Brussels, Belgium.

The format for the meeting in Brussels included reviewing responses to recent experiences from different perspectives, including patients, including regulators and policymakers. These presentations included case studies' responses to variant CJD, West Nile virus, parvovirus B19, and SARS.

From the discussions of the presentations, five key areas in the management of emerging infectious diseases were identified. The five areas included risk assessment, manufacturing process testing and pathogen clearance, donor and recipient communication, donor management, and

appropriate clinical product usage. Time was then spent in two breakout sessions to discuss the key elements that were identified.

We're working on a publication of our proceedings of our first roundtable, but in terms of outcomes, there are a couple of areas that were identified for further work. And like in real estate where location, location, location comes up frequently, the resonating concern by participants was in communication. So one step would be to continue to develop a structure for rapid and effective communication.

Also, a more lofty goal would be to find a venue to work towards developing a blueprint or a best practices guide to facilitate decisionmaking in the face of emerging infectious diseases.

In summary, PPTA has an existing structure to address and communicate issues related to pathogen safety of its therapies. PPTA has also initiated a venue to work on improving the global response to emerging infectious diseases. We appreciate the committee's willingness to undertake

this important matter. We would also ask that in your deliberations you balance the differences and similarities between transfusable blood and the plasma therapies, and also, as we've heard today, although your mandate is truly American under the U.S. Government, that you think globally since pathogens require neither passports nor visas to cross boundaries.

Thank you.

DR. BRECHER: Thank you, Mary.

Any questions or comments?

[No response.]

DR. BRECHER: All right. Our next speaker is Shannon Penberthy of MARC Associates. She's a consumer advocate for the National Hemophilia Foundation, and she's going to present the view of the consumer.

MS. PENBERTHY: Thank you very much for the opportunity to present to you today. I am Shannon Penberthy with MARC Associates. We very proudly have represented the National Hemophilia Foundation for 20 years now in Washington, D.C.

This presentation, I must acknowledge, is a collaborative response. When approached to make the presentation, I was asked to incorporate the processes and concerns of the broader plasma user community, and I wish to acknowledge Miriam O'Day from Alpha One Association, Michelle Vogel from the Immune Deficiency Foundation, and Mark Brooker from the World Federation of Hemophilia for their contributions to my presentation.

We tried very hard to define what is our role as consumer organizations in the process, and we defined that mostly clearly as our role in advocacy both with Congress and with the agencies, our work with committees such as this one, and obviously advocacy with manufacturers in terms of seeking information about viral inactivation, advocating for the safest products that we could have, given current technologies, but also our very broad role in terms of information that we provide to consumers and medical providers.

One of the commenters who very kindly reviewed my presentation recognized that our roles

are very much predicated on the communities we represent or the end users of these products, and we remain the front line for anything that might occur from--whether it be a manufacturing--something that happened in the process to the biopathogens. And that gives us an unequivocal role as part of the blood safety process.

Rather than trying to review what each of our individual organizations do, we provided kind of an overlay of the types of activities that we do. Obviously, we monitor information that comes to us from a wide range of sources that we've listed here, both agencies, manufacturers, news reports, individual consumers, sometimes our chapter organizations, obviously our physicians, and more and more from foreign governments.

It is interesting, I could almost name an example in every case where information first came from one of these sources, so we have to continue to cast this broad net. There's no formal process.

Obviously anytime we get information, we do investigate it immediately. Each of our

organizations have conglomerations of task forces that both include consumers and medical input. Most of us have medical and scientific advisory committees that we also consult.

Because of the broad net, we're getting information from a lot of places, and we try to verify that information and help assess that information by also using that broad net. So that means consulting with the federal agencies. Increasingly, we get information from consumer organizations in other countries and government organizations from other countries, but also consulting with the manufacturers, and that could be with the individual manufacturers or through PPTA.

The next step is probably the most difficult for us, and I'd like to echo some of the things that Karen said in his presentation. We are very much faced with this tension and with the responsibility to communicate information in a world where we don't always know the answers. In fact, very much that--much of what we have to work

with and what we do is predicated on the need to act in the absence of medical evidence or even guidance.

I think that because of the events that have happened in the '80s, it's a responsibility we take extremely seriously. And yet it always makes us nervous maybe the two days that it takes between the time the information comes and the time that we're able to investigate it, get a clearer picture of what's happened, and determine how to communicate that to our communities. It's a role that carries not only the responsibility, but also potentially considerable liability.

We do communicate through medical advisories. Those are usually sent through electronically, posted on the websites, and in serious circumstances I'm sure we would also do mass mailings. We follow up with those with articles and electronic and print publications, information to our chapters, information to the hemophilia treatment centers, or other physician networks that are in place for the other

organizations. We're really trying to get out the information as much as we can.

Finally, our step is advocacy, seeking remedies when there's specific concerns, participating in the blood safety policy decisions and discussions, particularly through the committees where we all have representation now, all the consumer groups, and then educating consumers both on disease and incident-specific information. I think one of the biggest challenges is trying to put information into context, so you don't want to overly raise alarm and yet you want to make people aware and finding that balance and being able to clearly communicate information in the absence of, you know, guidance and the absence of full knowledge. There's still a lot of unknowns, obviously, with blood products.

Our conversation when we had our conference calls to prepare for the presentation, we focused somewhat on what our organizations do, and I've just kind of gone over that, but also on what our concerns are. The discussion went to

these points very quickly. The process is often informal. It's often dependent upon organizational, in some cases individual relationships rather than set regulations or processes. We're not always sure that it's structured to respond very rapidly. I mentioned that sometimes it takes a few days before we hear something that may even come as somewhat of a rumor and that we have to investigate and then determine whether this is something that needs to be communicated and what's the appropriate way to communicate it.

We also collectively thought that the lack of more formal post-market surveillance hampers us in some cases in terms of better understanding of product interactions and outcomes, and also as an alert system. We're very fortunate in the hemophilia community to have a surveillance system through our hemophilia treatment center network, and I know that other groups would love to have that same kind of surveillance. They have their own networks in place that try to mirror that. But

even then, if you're not reporting, if you don't know what you should be looking for, then you don't get that evidence coming out. And that was something that we discussed as a concern.

Then also the lack of international collaboration and I could even add harmonization to that. There was recently an incident in France with the identification of the--I think it's the ninth vCJD donor where a company--one of the manufacturers of plasma products took it upon themselves to go do lookback, but that wasn't something that was required under French law.

We also had, I guess, recommendations. I think we are--we want and need assistance in terms of raising consumer literacy about blood and blood product safety, about informing our consumers about the disease and incident-specific information and providing guidance. I know there's going to be discussion of this later this afternoon in terms of the case examples, but I think the vCJD is a good example, particularly the U.K. notification that went forward to patients and consumers in the

United Kingdom, but wasn't widely disseminated to other governments, to other consumer organizations in the hemophilia community. And it left us, you know, with a question mark in terms of did the guidance that was put forth to consumers in the U.K. need to be applicable to consumers in the U.S. who might have used those products. How would such guidance be implemented in our health care system? Those are questions that still remain for us.

Lastly, we recommended that there be improvements in enforcement of post-market surveillance. We certainly understand all the reasons that companies might not want every single incident reported. But we feel there must be a balance there because we do feel that we're perhaps missing information that could be very useful to us. Obviously enhancing patient notification, we do have the patient notification system that's maintained by the companies, and yet it continues to not have full enrollment, and we need to continue to explore ways of making information widely and quickly available to our communities.

Lastly, recognized the importance of a multidisciplinary approach to risk assessment, including bioethics. We have noted that many of the advisory committees at one point or another had bioethicists as members, and that seems to be something that's missing from may of the committees now and something we thought the committee might take under consideration.

I know that Miriam and Michelle would be glad to help me answer any questions, and I'm sure that Mark Skinner would be glad to (?) Federation.

DR. BRECHER: Questions? Comments?

[No response.]

DR. BRECHER: All right. Thank you--oh, Jerry?

DR. HOLMBERG: I just wanted to make a comment on that last comment that you made. This is a recognized shortcoming, even on this committee, and we are working to try to overcome that. So your point is well taken.

MS. PENBERTHY: Thank you.

DR. BRECHER: Okay. We're going to move on to Matt Kuehnert, who is Assistant Director for Blood Safety, Division of Viral and Rickettsial Diseases, National Center for Infectious Disease, Centers for Disease Control and Prevention, and a member of this committee. He's going to give us the CDC's strategic approach.

DR. KUEHNERT: Thank you very much, and good morning. Today I'll briefly describe CDC's role in responding to microbial threats to health and suggest ways that blood banks, transfusion services, industry, clinicians, and transfusion recipients, which I'll refer to as a group as "the blood community," can work together with CDC and other public health partners to improve transfusion safety through a strategic plan.

Starting with the IOM report in 1993 that was discussed previously, this group reported an alarming increase in emerging infections and recommendations to address these threats over ten years ago. And to implement these recommendations, CDC designed a plan to respond to emerging

infections, including a component for blood safety.

IOM's most recent report on microbial threats to health again emphasized the global factors leading to emerging infections and brought to light some new issues to consider on blood safety. Here are some of these factors which, again, our IOM contact previously described. Just to go through briefly, some of these factors include: microbial adaptation and change; human susceptibility and infection as individuals become, particularly immune deficient, more susceptible to a wide array of infections; an explosion of advances in biotechnology and industry; breakdown of public health measures, or at least a failure to keep up with the evolution of populations and of advances in technology; war, famine, and natural disasters which further weaken public health infrastructure; and, finally, apart from the random forces of nature, human intent to harm in the method of bioterrorism threats.

All these changes are relevant to a wide array of topics, including blood safety, and all

these elements can create a potential perfect storm, resulting in increasingly new opportunities for transmission through biologic products, including blood.

I wanted to just go through briefly how a public health microbial threat is generally approached. There are a number of standard questions that arise depending on the setting, and first and foremost is it traditionally infectious, is it transmitted from person to person?

Next, is it transmitted through use of donated biologic tissues such as blood but not only blood? Also organ transplants and tissue transplants sometimes make us realize that there are pathogens that can be transmitted through biologic tissues, and we need to be aware of those.

Next, what is the sort of mechanism? Is it an endemic threat that's been around for a long time and for some reason has reached a certain threshold? Is it an epidemic threat? Is it globally imported? Or is it a theoretical threat such as a bioterrorism threat?

I think one thing to keep in mind if all these--or if any of these criteria are filled, is there an available and accurate diagnostic test? Is that something that has also been an obstacle in addressing a microbial threat?

Finally--and I don't want to say that this is the least important because perhaps it's the most important--what is the impact on recipients? Is it a true pathogen? Does it cause disease? And in what population is there specific recipients who develop disease? Or is it a wide array of recipients that are at risk?

The recent concerns in blood safety are myriad. These have been covered fairly well today. Some of these pathogens illustrate some of our successes in public health, but also some speak to gaps for a need for a comprehensive approach, including prions, viruses, bacteria, parasitic diseases, and the unknown, which can be in any one of these groups.

I also want to touch briefly on non-infectious threats. White particulate matter was a

problem that we didn't know what the scope was initially and needed a way to approach that. Similarly, concerning leukocyte reduction, filter-associated phenomena, are there patient reactions that result from them? It's something that's an important question that has come up in recent years.

So the IOM in their report on microbial threats to health was charged not only to assess the current state of knowledge, but also to identify potential challenges and opportunities for public health action, and some of these were mentioned today, but I just wanted to highlight the ones that I think are very relevant: to improve disease through better reporting; to explore innovative systems of surveillance, which I think some of the blood donor data could certainly fall under that category; developing and using diagnostics; educating and training a multidisciplinary workforce; and having a comprehensive infectious disease research agenda.

CDC has a patchwork of programs to address

many of these concerns for blood safety, but there is no central research activity for blood safety at CDC. So that many programs which are disease oriented have resources focused on these issues. Many of these efforts address important questions in both transfusion safety and public health, but gaps remain, and just to go through these briefly, we have surveillance efforts for transfusion-transmitted CJD, efforts for research on HHV-8, which will be presented later today; surveillance for transfusion-transmitted viral hepatitis.

I'll talk a little bit about the ones that are set apart in yellow here: West Nile virus, malaria exposure risk assessment. We have research efforts on babesia and Chagas, assessment of transfusion-associated sepsis. I'll briefly touch on white particulate matter and the effort there, and universal data collection on thalassemia data projects. I'll briefly outline that, which is an activity of the Division of Hematologic Blood Disorders. We also have efforts in global AIDS programs, program initiatives in developing

countries, and also have ongoing collaborations with other federal agencies such as NIH on linked blood donor-recipient repository and radar.

With all that said on activities, we need to do more, and CDC is the nation's disease prevention agency. It's changing to meet the challenges of the 21st century. This effort for reorganization is called the Futures Initiative, and modernizing CDC's approach will enhance our impact on health, support our capacity to respond to public health emergencies, and directly engage the public and external partners who are recognized as our customers.

Just to go into this in a little more detail, the CDC's reorganization is designed around principles of goals management and follows principles of strategy and goals development derived from a population health assessment. Goals management driving public health priorities and allocations, an emphasis on research and innovation, an emphasis on health protection marketing to the public, and consolidation.

This approach recognizes that it's our customers, defined as the population at risk, and external partners that should drive CDC goals and not internal research interests. And this is just a schematic to emphasize that, that it's the customers that should be on the top that drive the research agenda and drive public health activity and not necessarily the inner workings of the agency.

So in focusing on the right side of the columns here, the activities should be focused on and the goal is to have them focused on clearly articulated goals and performance measurements, a defined segmented customer approach, and a strong public health partner network.

We as the blood community need to be concerned about transfusion recipient health and specific goals and outcomes that need improvement, and also to identify the partners to public health that will achieve change.

A good example of this approach is taken by our Division of Hereditary Blood Disorders,

which uses a model based on public health concerns, seeking input from community-based organizations, and specialized health care centers to prevent and reduce complications in a specific population.

Another collaborative effort in this is the Universal Data Collection Program, whose purpose is to monitor blood safety among product recipients, monitor extent and progression of joint disease, and identify issues for further study. This is one example, I think, of a population-based approach that I think is a good example.

I just wanted to also touch on some collaborations between the blood community and public health, but where challenges remain. West Nile is an example of a known pathogen that became problematic in the U.S. through a large epidemic. And the spread of the West Nile virus is monitored through a system called ArboNet, which most of you are familiar with that. It's a realtime reporting system developed by CDC and state and local health departments.

Thousands of donations have been

interdicted found to contain West Nile virus, but also there's an ancillary benefit. Blood collection agencies have worked closely with state health departments and CDC to share data that goes into ArboNet, which is an invaluable addition to human disease surveillance. This slide shows the geographic distribution of donors with presumed West Nile viremia from blood screening in 2003. Note the distribution. This distribution in the United States closely mirrors that of neuro-invasive disease, particularly in the Great Plains area. But the remarkable thing is that in many counties, the blood donor viremias preceded a neuro-invasive disease so that the viremias were the first indication of human illness in many of these counties and provided an important potential early warning that transmission was occurring.

So this is something we should consider focusing on, how blood donor data can be shared with public health authorities to predict disease outbreaks and contribute to surveillance.

There is also the flip side, which is--I'll use malaria as an example, where current donor deferral policies are confusing to blood collection centers which sometimes results in ineffective screening. They need the newest public health information in order to adequately operate. So to help address this, CDC is currently engaged in a mapping project so that people who need the information in a certain location, concerning a certain location of exposure can immediately access it.

More generally, blood centers are increasingly plugged into methods for public health information dissemination such as the Health Alert Network, which is a public health method of information dissemination that is critical in emergency notifications.

Finally, just as far as the examples, I wanted to touch on white particulate matter, which is a phenomenon that later was identified as clump cellular fragments, but at first it was really unclear what it was and what implications it had on

blood safety. And a critical question was whether

this phenomenon was causing adverse reactions in recipients.

To answer this, the Georgia Health Department and CDC conducted a statewide survey to look at trends and reactions over the past year and in the month the problem was detected. And we didn't see a dramatic change in reaction rates, which helped to reassure that this was not a phenomenon with widespread clinical relevance. But it also highlighted the need to have existing surveillance systems for adverse reactions in place and to link this with other factors such as factors in processing, such as the ones that were shown to be associated with white particulate matter.

So this, again--and I'd also expand this to thinking about this in terms of problems that come up from time to time concerning leukoreduction filters, that what we need is prospective surveillance to look to see whether there are adverse effects on recipients.

So as we approach new problems, CDC activity should be based on an iterative process of

data collection through surveillance, identification of factors and outcomes that define a customer population, and using results to explore further study and new prevention methods.

Again, to touch on the IOM recommendations, we really need to look at a broader perspective. The only way that we can tackle many of these issues in a resource-challenged environment is with a comprehensive approach where one intervention can result in a leveraged outcome improvement for an entire population or group of populations.

I just want to touch on the fact that, sure, infectious diseases are a very important risk to keep in mind, but there are non-infectious risks that also need to be kept in mind, and that an overall program concerning the adverse event surveillance might be the best approach, and some interventions that have been suggested, I guess the best way I could summarize it would be having transfusion optimization efforts at the hospital level to promote the safe and effective use of

transfusions, track hospital performance through active surveillance, error reporting, really benchmarking, which is of growing interest in patient safety, and to educate clinical staff on appropriate usage. And many hospitals already do this, but to really emphasize these efforts, to oversee proper implementation and cost/benefit of new technology.

I also want to touch on the issue of a broader perspective concerning biologic products. This is a slide that is of nerves in a transplanted kidney. It was part of an investigation of a group of organ transplant recipients with encephalitis. It turned out to be rabies transmitted through organ transplant. And although rabies may not have direct relevance to blood safety, there are other organisms that likely do, and there are many examples of pathogens transmitted through organs and tissues that need to be considered in terms of blood safety, so that when you think not only about hemovigilance but also, to coin a term perhaps, biovigilance, looking at blood in the context of

organs, tissues, and other products derived from human and animal sources.

So to sort of summarize, I think in identifying the gaps, the lack of a research activity exclusively centered around blood or tissue at CDC necessitates a cross-cutting approach to the problem. We have a blood, organ, and other tissue safety working group at CDC which interacts with other agency task force and committee groups to assess gaps for intervention. I guess we have to just--I just listed some of them here, and there are others that were presented today. We really need to consider how all these fit together to develop a cohesive strategic approach.

I think if I were to sort of emphasize the content issues that need to be considered, we need to look from the beginning point at donor collection to laboratory test diagnostics, to transfusion services, to clinicians, and to public health in terms of donor assessment and management, in terms of recipient assessment and management, in terms of diagnostic test development, in terms of

implementation of new technologies, and looking at stored repositories for emerging threats.

And so in thinking about surveillance, there's sort of a central pillar you could see here of the denominator data, which is very important. I think the department is taking very important steps to be able to capture this. And then there's sort of two, I think, separate pillars. There's the unusual events to detect emerging infections where I think we need a very robust and sensitive surveillance system to look at fatal clusters and an emergency approach for confirmation in terms of epidemiologic and laboratory investigation. And then, but also more common events, to have an infrastructure for common event surveillance, focusing on routine events and benchmarking.

So just sort of, you know, broad strokes, what's needed is relevant expertise, external partnerships, priority development, data coordination and communication, words that are all easy to say but are really quite complicated as we move from, I think, what is the mission of CDC to

look at risk assessment to then move into a purview of regulatory agencies in terms of risk management.

So, to summarize, the CDC's strategic approach on blood safety is a patchwork of programs where it is essential for coordination. We've had successful responses to emerging threats and a mission that's focused on risk assessment and communication. But there really needs to be an overall strategic approach to be able to prioritize these efforts. We also need to take a broader view looking at organ and tissue safety as well and include them in a comprehensive approach.

Finally, there needs to be efforts to look at interventions to improve--whether you call it hemovigilance or biovigilance, depending how inclusive you want to be, to specifically define transfusion and transplant recipient health goals and outcomes, because this is something that CDC is going to increasingly focus on, and I think that the overall government will increasingly focus on in terms of goal management, and to collaborate as a community and define the community. It's very,

very positive to see advocacy groups involved with this, but I don't often see advocates for certain transfusion populations, and that's very concerning because I think they're underrepresented, and somehow we have to find a way for them to have a voice, because I think the advocacy approach is very important, and I think that is missing in some segments of the population.

Thank you.

DR. BRECHER: Questions? Celso.

DR. BIANCO: Thank you for a very comprehensive review, Matt, and for being so candid about the issues that you have within CDC. But in an ideal system, what would be the role of CDC? What would be our role on the other side of the fence? The only role that is well defined here is FDA that is to make rules.

DR. KUEHNERT: I understand, and we're not going to become regulatory, so that is not a role that we're going to have. So let me just set that apart right now, and I'm not suggesting that.

But what I am suggesting is there are

certain partners that we have that certainly is within our mission, and that includes what we discussed earlier concerning public health partnerships. I think what was discussed before about there being a need for better communication between blood banks and public health is a very, very important one, because I see both sides of it. I see a blood bank say, well, you know, we don't understand why we need to interface with the public health community on this. Then you sort of explain how this is--you know, let's explain this in terms of HIV, and then a light bulb goes on and I understand now why there's a need for reporting.

On the other hand, the public health institutions also need education about why they need to interact. I think when there's an emergency such as SARS and some other things that have come along the pike in the past few years, there's an immediate need to communicate. But we need to really strengthen those partnerships in times of non-emergency.

The other issue where I think CDC can

really play a role is in terms of what's been called the end user, but also the health care providers that care for the end user. And I think that we have special partnerships with clinicians, and I think that's an area that I think should be looked at closely and how we can reach clinicians better.

DR. BIANCO: Another point following the same thing. One thing that you didn't mention but you have to work through the state health departments, and we saw very well during the West Nile epidemic the difficulties with this intermediate there and all that. How do you suggest that we address that?

DR. KUEHNERT: Well, I wouldn't necessarily look at--I would look at them as the primary partners where we are trying to enhance the relationships with them. I wouldn't necessarily look at them as an intermediary. I think they are essential partners. I think that's what we're missing here. We're missing a seat at the table, and I feel acutely the absence of Jeanne Linden

here because I think she is a very important example of someone who recognizes the need to have close public health and blood and tissue bank collaboration. But I think we need to include them as primary partners because you're absolutely right, we need them to be able to do anything in public health. And simply the role of, you know, the federal agency of CDC is to assist those public health partners in their activities.

DR. GOMPERTS: Matt, when I look at the issue of emerging pathogens, which is primarily what we're talking about today, the big question is how do you do surveillance of something that you don't know is out there. So the question that I have to you is how do you do that, although you certainly have given us some perspective as to the approach to current situations. But from where I sit, the biggest threat certainly looking backwards is HIV and HCV, and this is primarily because there's a substantial population out there with an agent that was primarily asymptomatic, that produced significant disease over the medium and

long term.

So if we look at the technologies that we have today that might be useful, the NAT technologies have certainly reached a particular point, the genomic--the approaches and using probes and chips and so on, to use these technologies to screen for classes of viruses, because there are going to be sequences that are common to agents within a particular family and so on. Is this type of technology being sorted out and applied?

DR. KUEHNERT: Well, I think, you know, again, with sort of the way that most research activities are pathogen based at CDC, there are many, many efforts to look at so-called pathogen discovery. And I think that's something we really need to plug into concerning blood safety, that this is a real issue that needs to be focused on.

I don't have a good answer to your question. I think that we can look at research efforts for markers, biological markers in repository samples to constantly look for new things. But we're still going to miss things. I

think as a safety net, I want to go back to that surveillance approach and that hemovigilance approach because that looks at, you know, things that we traditionally see as infectious, or even non-infectious, because it really focuses on outcome. So if we see in a certain segment of the population that there is not the outcome that we expect, we need to investigate that. The way it is now, we depend on astute clinicians to be able to say, well, that's not an outcome I expected, and it could have been from that transfusion. But that doesn't always happen.

So I think, you know, there needs to be some sort of a safety net for surveillance, and, you know, that I think with that sort of bimodal approach of looking at the research approach and looking at the outcomes, I think it's--I think will create synergy and we'll have at least less gaps taking that approach.

DR. BRECHER: Okay. Anybody else?

[No response.]

DR. BRECHER: All right. Thank you, Matt.

DR. KUEHNERT: Thanks.

DR. BRECHER: Our last speaker for this section is Dr. Ed Tabor. He's the Associate Director of the Office of Blood Research and Review of CBER, FDA, and I should also mention that he has worked closely with the Emerging Threats Subcommittee of this Advisory Committee, so we thank him for those efforts.

DR. TABOR: Good morning. I'm going to speak to you today about really what is a U.S. Public Health Service program for addressing emerging infectious diseases that could threaten the blood supply.

We've already heard a little bit this morning about why emerging infectious diseases are a particular problem today. I think one of the biggest causes of this is international travel, travel between dense population centers, and travel to remote or undeveloped areas where various agents are more likely to emerge as human pathogens. We also heard today that the increased populations in the cities are an important factor, and this is

certainly true. The increased populations in the cities mean there are greater reservoirs in which agents can emerge.

And then combined with these are the cultural changes that have occurred, things that we as people do and things that different segments of the human population do that make it easier for agents to emerge. You've already heard this morning about the fact that some populations use different animals for food than we're used to in the United States, but there are cultural changes in the United States that have been factors as well, such as the rise in parenteral drug use for recreational purposes in the United States, changing sexual mores, and so forth.

And, finally, environmental changes such as deforestation and the dislodging of animal species can contribute to the emerging of infectious diseases.

Now, you can look at emerging infectious diseases in a bimodal sense, and to do this I'd like to borrow two terms from cancer etiology,

initiation and promotion. One can think of initiation of an emerging infectious disease as either the jumping of a species barrier from animals to humans or the achieving of a new level of virulence of an agent. And one can designate as promotion the dissemination of the agent due to cultural changes in the human population.

Well, what makes an emerging agent a threat to blood safety? It's obvious that symptomatic donors would be perhaps too sick to feel like donating or would be excluded by the donor questionnaire or by having their temperature taken. But an asymptomatic donor who might be viremic or bacteremic could be accepted for donation, and this could be a donor who's either in the incubation period of a disease or the window period or someone with a chronic asymptomatic infection.

In the Public Health Service agencies, we have several goals in our approach to emerging infectious diseases. First of all, we'd like to anticipate the emerging agents that could threaten

the blood supply. We want to monitor reports of emerging agents and see if they might infect the blood supply. We want to evaluate the degree of the risk for the blood supply and blood safety. And, finally, one of our goals is to try to focus PHS funding and lab resources on dealing with these threats.

We've really taken three major approaches. One is the Emerging Infectious Diseases Committee, of which I am the Chair. Second is the creation of a database of agents that could threaten the blood supply. And, finally, the development of a paradigm for coordinated PHS action to deal with any emerging agent that could threaten the blood supply.

The Emerging Infectious Diseases Committee reports to the U.S. Public Health Service Interagency Working Group on Blood Safety and Availability, which is also known as the PHS Blood Conference Call. It involves many federal agencies meeting once a month to deal with blood issues.

The Emerging Infectious Diseases Committee

itself has representation from CDC, FDA, NIH, and the Department of Health and Human Services. It was started in 1997, and we have quarterly meetings, but we also have ad hoc meetings to deal with reports of new emerging agents that could threaten blood safety. We invite subject experts from within the PHS to address issues that are on our agenda. And we also have a variety of PHS personnel who attend as observers. We try to identify questions that need to be answered and to identify problems that we need to address, and we try to find lab resources to do this.

When we are addressing one of these emerging agents, we first try to determine what intramural studies at CDC, FDA, or NIH are already being done on the agent and, in addition, what intramural lab resources can perhaps be redirected to doing work on the new agent.

We also try to find out what extramural studies are being funded by NIH. Usually this is NHLBI, but it also involves other institutes. We try to identify what serum repositories exist.

Again, it's usually through NHLBI, but through other sources as well. And, finally, try to identify whether new extramural funding might be available that could be targeted toward the agent.

The second of the three activities is maintaining a database of infectious agents that could threaten the blood supply. This database for each of the agents contains the incubation period for blood transmission, the level of disease severity after blood transmission, the estimated transfusion risk in the United States, and whether any preventive measures are available such as through the donor questionnaire or serologic tests. At the present time this database has 29 viruses or virus groups, 11 bacteria, 8 parasites, and 2 prions.

The third thrust of our activity has been to develop a paradigm for coordinated action on emerging infectious diseases. Basically this paradigm involves a lot of common sense, but here's a description of what we generally do. We try to find reports of new infectious diseases, either in

the scientific literature or in the lay press or through scientific contacts. When we identify one of these potential new emerging agents, we try to establish what is already known about the agent and its epidemiology. We do this through literature searches, through input from subject experts within the Public Health Service, and for many of these more exotic agents, the input from the experts is often the primary source, and, finally, in some cases through field investigations by CDC.

We try to establish what the risk is for blood safety. We try to determine if the agent is bloodborne, whether there is an asymptomatic period when viremia or bacteremia is present. We try to determine what the prevalence is among blood donors and whether there are known risk factors that could be criteria for donor exclusion.

In laboratory efforts, we determine whether there are serologic tests or nucleic acid amplification tests that could be ultimately used for blood screening. We try to obtain field samples to test, and when there are archived

samples or repository samples that would be appropriate, we arrange for testing of these. These would include donor-recipient paired samples, which are available through some of the repositories, and also linked donor samples so that donors could be contacted for follow-up testing.

We identify laboratories inside and outside the government where testing could be done, and where there's no available test, we try to encourage test development.

Finally, we make an effort to communicate with interested parties about the emerging agents. We do this through interactions with the blood and plasma industry, through the organizations such as the AABB, ABC, the Red Cross, and the PPTA. We communicate through letters, official letters to blood and plasma establishments. We conduct scientific workshops. We make presentations at the Blood Products Advisory Committee, and we develop guidelines when appropriate.

Before closing, I'd like to just mention that the members of the Emerging Infectious

Diseases Committee are myself, Dr. Kuehnert, Dr. George Nemo from NHLBI, Dr. Harvey Alter from the Department of Transfusion Medicine at NIH, and Dr. Paul McCurdy from the Department of Health and Human Services.

Thank you and I'd be happy to take any questions.

DR. BRECHER: Celso?

DR. BIANCO: Ed, thanks for this nice overview. You didn't show the list.

[Laughter.]

DR. TABOR: Well, first of all, half seriously, I'll say if I did show the list, the print would be very small when projected on the screen. But the list hasn't been--obviously we'd be happy to share it with the committee. The list hasn't been made available for public distribution as of the present time, not because there's anything secret on it but it hasn't been cleared through all the appropriate offices for public distribution.

I think because it includes a lot of

factual information that's based sometimes on unpublished work that's done in laboratories that are dealing with some of the more unusual agents, there are a lot of people within the involved agencies who would want to be sure that everything is highly accurate before it's released. Obviously, if it were desired to release it, we could certainly arrange that, but it would take a little work to get it cleared, I think.

DR. BIANCO: I think just as a closing, I think it would help--you did a tremendous amount of work on that, and for a good while, and I think it would help us focus on those agents and think about them as things happen.

DR. TABOR: I'd like to just mention that I don't know how many--several of you certainly have served on other committees where we discussed our counterterrorism preparations, and we have a separate list--obviously there's some overlap with this list. We have a separate list of agents that could be used by bioterrorists that could threaten the blood supply. But this one is really any agent

that could threaten the blood supply. And if the committee asked for it, obviously we'll make an effort to get it--we'll certainly get it to you promptly.

DR. BRECHER: Okay. Thank you, Dr. Tabor. We're going to go into discussion for a little while and also open the floor to any questions for the speakers this morning. I know Mark had one question that did not get addressed. Maybe we'll start with you, Mark.

MR. SKINNER: Thank you, Dr. Brecher. I guess just a question and a general comment because I'm not sure time really allows to answer the question that I had.

I had hoped that when Roger made his presentation this morning, when he talked about what we know is--or don't know is about transmissible in transfusion, that we would also have just the basic understanding of then what is further transmissible or not in the plasma-derived products, and I think that would be very helpful because there's certainly only a subset of those

that would be further transmitted.

And I had asked for a similar list back when we received the presentation I guess about a year or so ago on the biological agents, what would be transmitted in the plasma-derived products. And so we really haven't received it either time, so perhaps coming back to that at some point.

And then the other part that I would note was missing from a number of these presentations, again, as we go through the emerging infectious disease paradigm, as it relates to the blood supply, certainly for those populations that are dependent on the blood supply, it would certainly be helpful to have--or some knowledge how the process works then to further evaluate whether it's transmissible in the plasma-derived products. And that could have been added to the FDA presentation as well as some of the others.

So, you know, in lieu of going back and asking the specific presenters to answer that, unless any of them want to comment on it now, I might suggest that when we continue this

conversation at a subsequent meeting, we look at how this discussion extends to the plasma user dependent community.

DR. BRECHER: Would any of the speakers like to address that? Perhaps just a question to Dr. Tabor. Is that information included in your database, in your list?

DR. TABOR: First of all, let me say that we're very sensitive to the issues of plasma safety and safety of plasma derivatives. The situation with plasma is obviously a little different because of the manufacturing processes offer some level of protection against at least some agents, and the introduction of inactivation and removal procedures, a couple of--perhaps it began in the mid-1980s, has also changed the picture for at least some agents. And certainly--I realize I'm telling you something you know, but certainly for hepatitis B and hepatitis C and HIV, these procedures are certainly very effective. Obviously for some of the newer agents, they are known in some cases to not be fully effective.

This database really focuses mainly on blood. I think the agents that are still of concern for plasma derivatives really are a subset of this, and some of the characteristics of the infections that you would put on a database for plasma derivatives I think would be a little different. So for that reason, we actually--when we started this out, there was some information about plasma derivatives on this database. But it became too complex to keep together.

MR. SKINNER: Mark, can I just make one comment? And I appreciate that. I recognize that it is only a subset, and the plasma products that we use today have a very robust clearance and activation process, and for most of the agents that were talked about, it's not an issue. But having that information and understanding where the points of focus are I think would be helpful, and I guess the point in raising it is that I would just hope the discussion when we talk about paradigms or the other kinds of communication chains, that the discussion just doesn't end with blood and that we

recognize that there's users on down the stream.

My question has really been answered. If we can just think about it for a future topic, I would appreciate it.

DR. TABOR: If I can put some additional words in your mouth, I think what your real concern is that risks for plasma derivatives be high on the radar screen. And certainly at the Emerging Infectious Diseases Committee meetings, plasma issues and plasma product issues are very high on our agenda. I can see a way that an additional database for plasma might be useful.

MR. SKINNER: I recognize that they are high on the screen. I'm involved in many of the processes. What I'm not sure is that it's communicated to the general public and all the other organizations. So I think when we're disseminating and educating about the process, I just want it to be mentioned.

DR. TABOR: Those are good points.

DR. BRECHER: It's my intent as Chair that the two subcommittees will continue and they will

continue to input into the agendas of future meetings. And so I will just charge the Emerging Threats Subcommittee to specifically address that in the future.

Any other questions for our speakers perhaps? Andy?

DR. HEATON: Yes, I had a couple of observations. What we're looking at here is the advance identification of risk through the review of sentinel events. Normally when a disaster emerges, there's nearly always a sentinel event which precedes whatever the disaster is, an infectious disease disaster or a physical disaster. And I think we've heard a good series of presentations from CDC and now from FDA about the process of monitoring sentinel events and then reviewing their implications.

I think one area that I would like specifically Ed Tabor's perspective or the FDA's perspective is on who should be on the emerging infectious disease review group. At the moment it's focused, it has CDC on it, who would be

appropriate to identify an emerging infectious event. FDA is clearly on it because they're the center of reporting mechanisms. But, you know, one of the issues we've just heard is that it might be prudent to have some form of plasma representation on it since there's specific implications for the plasma industry that could be reviewed profitably further up the chain of decision. I also think transfusionists or practicing clinicians--I don't know to what extent they're represented on this. And then, finally, your capacity to respond to the disaster is dependent on your ability to either come up with a new test, produce a pathogen reduction, introduce a new plastic, or introduce a new process. Many of those developments have very long lead times and require very significant dollar investments. And so another area where I think the risk assessment process could be improved would be the inclusion of appropriate manufacturing input or representation so the corrective action program, at least the implications of it can be considered as the sentinel event is assessed.

So I would suggest that the EID approach is a very good one, but it might need to include a slightly wider audience depending on the event being discussed in order to improve the quality of planning.

DR. TABOR: Well, first of all, we do have a transfusionist. Dr. Harvey Alter is on the committee. I think perhaps what you're suggesting is something that's larger in scope than what we originally conceived of with this committee. And it's certainly something that could be discussed.

The purpose of this committee is to evaluate those sentinel events before they're more than sentinel events. And so what happens in terms of developing assays or marshalling the entire blood and plasma community is further down the road.

I think what you'll see in the presentations this afternoon, that type of thing, as you well know, has happened, for instance, West Nile virus. But the purpose in designing this afternoon's program was to give some case examples

so the Advisory Committee can evaluate how well the system is or is not working.

I think it certainly would be reasonable for you to discuss, you know, whether you think this committee that we have should be expanded or changed in its design. At the moment it's a very small group. As I said, we often have very large numbers of people on the conference calls because we invite product experts. We have not to date that I can recall invited people from outside the government. Again, that's something that could be discussed.

DR. HEATON: I certainly support the concept of a filtering process and then expanding the constituents as the need arises. I just think you need to be quite careful when you do expand that to include those that will allow you to improve the quality of your planning process, and that's really my point.

DR. BRECHER: Ed?

DR. GOMPERTS: We've had a pretty good perspective this morning from a whole lot of

different approaches to the issues of emerging agents, but in my opinion, there has been a gap in that if one looks at the HIV situation, this was a new retrovirus. But retrovirus was known, and this theoretically from a scientific point of view, someone might have said, well, perhaps a retrovirus could jump across and infect humans, similarly with the coronavirus of SARS and so on.

So the discussion that I've not heard is in a situation of epidemics in animals, is there a possibility--for example, the dog parvovirus. There was a species jump from the cat to the dog. Is there a possibility of that particular agent making another species jump? There is a--the RNA viruses, the dengue West Nile group, there is a possibility these agents are all over the place, across the world and the possibility of another agent coming across. So some forward-looking focus on particular agents, particular classes that have the possibility of making the jump to human populations particularly becoming a threat to the blood supply and transmission.

So from a virologic, particularly virologic point of view, it would be useful to hear some strategies, some forward-looking strategies around that.

DR. BRECHER: Yes, hopefully, I think the intent of the afternoon session is to get some examples where we can see where we've succeeded and failed in anticipating these problems.

All right. If there are no other--oh, sorry. Go ahead, Paul.

DR. HAAS: It's just a quick comment. As I was listening from my perspective and my non-scientific training but the academic economics, I heard about training more public health experts, public health communication, more interdisciplinary approaches, importance of the state health departments, and my mind was immediately going to why there is such a thing that says public health as opposed to private health. And in a society like ours, where there's so much emphasis on the private market decisions, these types of things that we're talking about, the type of things Ed

brought up and all of the discussions, these are things that don't directly attract resources in the so-called market mechanism.

And I think one of the things that we might want to consider--and I don't have a magic wand to do this--is that there's a real need for resources out here to accomplish the types of things that we're listening to today. So if we make recommendations saying we want to do X, Y, and Z and don't say this requires an infusion of labor, capital, et cetera, to do it, not much is going to happen.

DR. BRECHER: Keep that thought because when we get to resolutions, I think that would be an important aspect of what we're going to do this afternoon.

All right. Well, we're going to break for lunch. We are going to start exactly at 1 o'clock, and we are going to stay on time.

[Whereupon, at 12:04 p.m., a luncheon recess was taken to reconvene at 1:00 p.m., this same day.]

A F T E R N O O N S E S S I O N

1:05 p.m.

DR. BRECHER: We're going to move on. We're now going to go to a panel presentation of Case Examples of Infectious Disease, and Dr. Epstein will be moderating this session.

DR. EPSTEIN: Thanks very much, Mark. I'm sure my chief task here is to keep the time and just to remind people of the structure of the program. We've progressed from a survey of the agents of concern and how they arise to a description of how the various governmental and nongovernmental organizations approach the problem of transfusion-transmitted disease, including emerging infectious disease. And now what we intend to do is provide a series of examples that hopefully will bring out different dimensions of the approach and try to illuminate gaps.

So the first of these presentations will be on West Nile Virus, and the presenter is Dr. Hira Nakhasi, who is the Director of the Division of Emerging and Transfusion-Transmitted Diseases at

FDA. Dr. Nakhasi is going to give us a West Nile update as an example of what might be seen as the model response, where the right elements seem to come together.

So, Hira, thank you.

DR. NAKHASI: Thank you very much, Jay, and thanks to the Committee in inviting me to present our update on the West Nile Virus.

It's really a pleasure to be here because usually you don't get to present such stories that much always. So it was one of such stories which has been touted very well the last few years, and I am glad I am the presenter for this one.

Just to give you background, many of you heard this morning from Roger Dodd a little bit about the West Nile Virus, just to refresh your memory after lunch, West Nile Virus is a single-stranded RNA virus and [?] virus. It's a mosquito-borne flavivirus and primarily infects birds,
occasionally infects humans and other animals, and most of the people, over 80 percent of the human infections, are asymptomatic and 20 percent develop

flu-like symptoms. Approximately, 1 in 150 infections result in meningitis or encephalitis. Advanced age is, by far, the most significant risk for sera neurological diseases. Viremic period can auger up to two weeks prior to symptoms and can last up to a month from the initiation of the infection, at least that was what was known when this epidemic started.

Now, in the 2002, as you heard in the United States, the first epidemic started in 1999. However, the first major outbreak occurred in 2002, which resulted in the identification of various modes of transmission, including the blood transplantation, breast feeding, transplacental and occupational per cutaneous injury.

Still, the magnitude of risk from West Nile from transfusion is unknown. The virus titer in blood is low compared to other transmissible diseases, such as HIV/AIDS, hepatitis and other infectious diseases. And IgM, in this case, once the patients recover or the IgM is developed, it can last up to two years. Unfortunately, there is

no chronic stage of West Nile infection reported so far.

Now, when this outbreak took place the first time in 2002, how did public health agencies respond to it, especially the FDA's response? First response was to provide guidance to blood establishments on donor screening and unit management to prevent transmission of West Nile by blood transfusion.

How did we do that? We, first of all, in August, I remember very vividly, it was the middle of August when this whole, actually, the paper was published at that time suggesting, from CDC, they published a paper suggesting that it could be transmitted through the blood. And then right at that time we issued an alert to blood establishments to exercise vigilance to exclude potential donors with flu-like symptoms.

Subsequently, in October, we issued a guidance to the industry for the recommendations of assessment of donors' suitability and blood and blood products in case of unknown or suspected West

Nile Virus infection to prevent donors with symptoms from donating blood.

Following that, in 2003, we revised this guidance, including the donors who were healthy, but then had symptoms of fever with headache within a week before donation because it was, at that time, predicted that it could be another symptom that if the people have a headache of fever and headache the week before, people can be prevented from donation of blood. However, that changed later on.

Next, we encouraged and worked with the manufacturers to develop suitable West Nile blood screening test. I remember that very vividly, in cooperation with the Department of Health and Human Services, FDA issued a call to industry to rapidly develop the blood donor screening test, and that was in September 2002, right after the epidemic broke.

Then, following that, FDA sponsored a public workshop in November 2002, where there was open discussion how to develop the West Nile Virus

donor screening test. And then we also discussed at various FDA's Blood Product Advisory Committees further how the tests would be developed, what are the main issues, donor issues, the implementation issues.

What FDA is also currently doing is developing reference material standards which the companies can use to validate their tests in a similar format. Many of you know that FDA has been participating, since then, with the AABB Task Force, which includes the other components of PHS agencies, CDC, NIH, others. We have weekly committees when the epidemic is in full swing. That is between June and November/December. Otherwise, we have biweekly meetings, also.

And while we discussed, basically, how to coordinate the epidemiological data, which the industry is collecting, the blood establishment is collecting, and also monitor how the epidemic is progressing.

Then, the other measure was the West Nile testing. The experimental kits in use are Nucleic

Acid Tests, which is NAT testing, from both human blood samples, and these tests are similar in format as that of HIV and hepatitis C. This testing is done for the whole blood, blood components, source plasma, bone marrow, cord blood, hematopoietic progenitor cell tissues, organ donors, and all of them are done under IND. As many of you know, the nationwide testing started under IND as of July 2003, and using two tests made by Roche, Chiron and GenProbe.

Clinical trials are being performed with those two tests, and the format is a pool of 16, in the case of GenProbe testing, and a pool of 6 in the Roche testing and also individual samples are being tested.

The regulatory path in West Nile testing includes all donors. Under IND, the products are linked to the West Nile test results. Then, there's a confirmatory testing is required, such as alternate NAT or IgM testing, unit, donor management, that is, follow-up, counseling and look-back is done in those under IND.

Then, what are the current recommendations for donor deferral at this time? As I told you, that in 2003 the revised guidance was issued which basically tells people not to donate if there are symptoms or having shown that they are infectious.

As you know, FDA regulation already is there that says if the person is not feeling good, they should not donate the blood. During the epidemic, which is we think between June 1 and June 30th, but it has been seen variable between, you know, sometimes the cases have been seen as early as April-May. But during this peak time, donors who report a medical diagnosis of West Nile infection are deferred for at least 28 days from the onset of symptoms or until 14 days after the condition is resolved, whichever is longer. Donors who report fever and headache a week before donation, are deferred for 28 days from the date of interview.

Then, in addition to that, another layer of safety is the pathogen inactivation. Available information indicates that it is unlikely that West

Nile is transmitted through plasma derivatives. How did we arrive at that conclusion? Because approved procedures for pathogen inactivations, such as solvent/detergent, will inactivate lipid-enveloped viruses, which West Nile Virus is, and model virus for Kleve viruses, such as HCV or West Nile, BVD has been shown as model, and it has been shown to behave like West Nile Virus in the process of inactivation.

In addition to that, experimental use of Psoralens, Riboflavin and Inactin for viral inactivation in plasma, platelets, and red cells also have been shown in inactivation of West Nile Virus more than four-log reduction.

Having done that and having all these things in place, what did it achieve? It achieved that we could start nationwide testing of West Nile Virus under FDA-approved INDs, which resulted in donations which were interdicted from asymptomatic donors with confirmed or suspected West Nile infection.

In 2003, when the testing started first,

818 West Nile Virus presumptive viremic donors officially reported to CDC or ArboNet. There are more than that cases in the blood establishments.

There were six confirmed transfusion-transmitted cases. Out of six, four had a very low level of viremia--.1 plaque-forming units per mL, as opposed to that when there was no testing going on in 2002, we had 23 cases of transfusion-transmittal, at least known cases. Who knows how many which were not known at that time.

As of January 11, 2005, on the CDC website, for 2004, there has been substantive reduction of the presumptive viremic donors. Only 199 were officially reported to CDC, ArboNet, both using MP-NAT, as well as ID-NAT, in areas because I will tell you in a minute that in certain areas, which were supposed to be hot, there was a trigger for ID-NAT so that--from MP-NAT could not detect those tests, and then the ID-NAT was initiated in those areas, starting May '04.

Because of that there was only one reported case of transfusion-transmitted cases,

which was only detectable by ID-NAT, and this case happened to be the case in Arizona when just weeks, I think four or five days before when the ID-NAT started. So I think that was missed because ID-NAT was not, you know, started right at that time.

Now, having shown that--let me go back to this slide. This is a very important slide because this had the cooperation between the industry, the public health agencies who could develop a test in less than nine months and could start testing the blood, which interdicted many, many cases.

Now, in spite of that, there are still some gaps which we need to understand because it's not totally home free yet because this is a model, which Mike Bush, Dr. Mike Busch, has developed. It basically highlights some of these gaps which we still are not sure where to put them. If you can see this one here, there is an initial period of a couple of days of infectivity when the level of virus is so low that it can be either detected by ID-NAT or it may not be detected by ID-NAT. So forget about the MP-NAT.

Then, the stage three, where there's a ramp-up in the infection, within six to seven days, that you can detect that--that's the time you can detect by MP-NAT, and 75 to 80 percent of the cases fall into that category, and that's what we have been able to detect.

And then when the virus infection goes down, then, at that time, the patient becomes IgM positive, and the levels of ID-NAT, the level of virus can be detected by individual NAT. And then, later on, it can be plus or minus with the ID-NAT, but the IgG is there, IgM is there. So the question is we know that the first phase, the first couple of days, when there is that ID-NAT-positive or ID-NAT plus or minus, that is infectious. Obviously, the MP-NAT not infect--well, the question is what happens when the IgM comes up? Is the residue of virus there? Is it infectious or not?

So some of the gaps in the current knowledge are, first of all, what we came to know during the follow-up of this patient, some of these

infected individuals, that viremia does not end at 28 days. In one of the cases last year, we found out that it can go all up to 49 days. So, remember, I said the recommendations was 28, the first donors should be deferred to 28 days. So having had that information now, we have to think about changing the next year, the deferral period has to be longer, maybe at 56 days, or what we know next studies may show a little longer. So maybe it has to be what will be the next information available. We may have to be changing accordingly.

Second, when the donors are re-entered, they are re-entered based on ID-NAT negative testing. The question is how long can you see them, how long after the infection you want to enter them based on the ID-NAT. There should be a time limit, and we had discussions with the AABB and others about these issues, and that is ongoing.

Then, the symptoms of West Nile infectivity. As I mentioned to you earlier, the year before the CDC studies had shown that there may be a correlation between headache and fever.

If a person is experiencing headache and fever a week before, then, therefore, there may be some correlation with infectivity of that person.

It turned out to be, last year when the studies were done, there was, by American Red Cross and other blood establishments, they could not establish that correlation. So I think the question is should we still be asking that question or not. So, obviously, that's another gap.

Then, the trigger for the ID-NAT because I said to you earlier that MP-NAT can pick up most of it, 75 to 80 percent, but then there are cases which the initial phases of infectivity or later stages of infectivity, which had been only detected by ID-NAT, what's the trigger which should be pulled from MP to ID-NAT? This year, that's last year, 2004, we, having had a dialogue with the AABB and other components of the Agency, we came up with a trigger that if there was an incidence rate of 1 to 500 or 1 to 100 in that particular area, one should start ID NAT testing. Is that adequate or not? We do not know. So, obviously, there is, to

reduce the risk of West Nile transmission, that needs to be thought more seriously about the triggers.

Even though it is very limited data available in human disease cases, there seems to be that there may be some variation, genetic variation in West Nile strains. The question is, if it is true, then currently available tests, can they detect those genetic variations? And if there is a genetic variation down the road, can these currently available tests be able to detect those things? So, obviously, we need to be thinking about that issue.

Then, as I mentioned to you, that what is the residual risk of West Nile infection in the presence of antibody? As I mentioned in that graph, there are times when patients could be MP-NAT low titer or MP-NAT negative or ID-NAT positive in the presence of antibody. The question is are those patients infectious?

Currently, studies are being planned with the NHLBI, FDA, and CDC and with the other core

components to develop an animal model system to see whether these samples, which we have these type of samples, are they infectious or not? So, obviously, we will come to know about that and whether we really need to worry about, once you have an IgM, even though there is a virus in there, a little bit of virus, whether that is infectious or not.

Finally, the usefulness of the West Nile surveillance data to predict epidemic. As you heard this morning from Matt, that they have found a correlation that maybe the people who are infectious viremic patients could give an indication that, in that area, that maybe the neurovirulence could be correlated with neurals. However, we do not know yet how that correlation stands.

In addition to that, as you know, there is infectious birds, mosquitoes, equine and symptoms in humans. Is there a correlation? Can that be a predictor, that if there is infection in birds, man, mosquitoes much higher in those area, will

that predict that down the road that would be a hot area or not?

And also the last question is the severity of epidemic from year-to-year. So, of all of these things, so, therefore, there are several gaps in the information. To end with the talk, I would like to acknowledge people who were involved in the success story, CDC, AABB Task Force, ABC, ARC, BSL, Roche, GenProbe, DOD and ourselves.

DR. EPSTEIN: Thank you very much, Dr. Nakhasi.

I think because we're running late and in deference to the other speakers, we'll just move on, and we'll take questions and discussion when we come to the panel session.

So it's my pleasure, next, to invite Dr. David Leiby, who is the Chief of Parasitology at the Holland Laboratories of the American National Red Cross, and he's going to provide a case example on Chagas disease, which perhaps illuminates an unmet challenge.

David?

DR. LEIBY: Thank you, Jay.

As you suggested, what I'm going to try to do today is talk about Chagas disease and give an example of why this remains an unmet challenge and perhaps educate us on how we might proceed with other agents of similar ilk.

As many of you know, Chagas disease is caused by Trypanosoma cruzi, which is a relatively small protozoan parasite. Natural infections are, in fact, vector borne. There's a nice picture there of the Reduviid bug that is responsible for natural transmission.

But here in the U.S., we're more concerned about other routes of transmission, in particular, congenital transmission from mother to unborn child, organ transplant, which was demonstrated several years ago in a report from the CDC, and, lastly, of course, what we're here for, blood transfusion.

Now, Chagas disease is endemic to Latin America, where it's estimated that 16 to 18 million people are infected.

When one wants to think about the implications of Trypanosoma cruzi infection on blood safety, we have to keep in mind that among blood donors who are infected, the infection is, in fact, asymptomatic, lifelong and generally thought to be untreatable. So here you have what I've heard talked about this morning, the asymptomatic donor who comes in, presents, and we don't know if they are infected.

What I'll try to do in the short time I have is try to highlight the transfusion risks or how we view them, as it relates to Chagas disease, and pointing out, in fact, that this is a, if you want to call it emerging disease or emerging infection in the U.S. that is driven purely by immigration issues.

I'll talk briefly about seroprevalence and how it is, in fact, influenced by donor demographics and how that, in fact, varies then by location within the United States.

I'll also talk briefly about the influence of intermittent parasitemia because that's very

important because, as many of you know, some of our look-back data was negative, but I think, in part, that can be explained by the types of blood products which were examined as well, more importantly, by the intermittent nature of the parasitemia.

I'll talk a little bit about transfusion cases, why few are recognized but, in my opinion, many are probably missed. I'll highlight possible interventions. And then I'll close, as a summary, with what I think are the barriers, at least in my opinion, as to why Chagas disease, the challenge has been unmet.

I pulled this picture, this graph down. This is actually from the 2000 Census Bureau. It's a rather handy, I think, map of the United States, which shows the percent of population of 2000 of Hispanic or Latino origin. As you can see from the color-coded bars on the lower right, you're going from a white up to what I consider is a dark-blue, purplish color and in between there's some yellows.

What's important, though, you probably

can't see from where you're sitting, the U.S. population is now 12.5-percent Hispanic. In fact, the Hispanic community, Latino community, is now the largest minority population in the United States.

If you look at this map, you can see a rather large concentration, of course, through the Southwest, even up through Nevada into the State of Washington, in Florida, up along the East Coast, though you can't see it because of the small size of the counties in this part of the country, but certainly all through the Northeast as well. And actually in many parts of the country, you find an increasing percentage of Hispanic individuals living in these populations. Of course, as we'll talk about here in a moment, those Hispanics are also blood donors, increasingly.

Now, this is a graph you've probably seen me use in the past many times from a paper we published several years ago in transfusion. At that time, when we looked at the seroprevalence rates in Los Angeles, the overall rate for our

study, out of a study of approximately 1.1 million donors, was that 1 in every 7,500 blood donors in Los Angeles were, in fact, infected with T-cruzi.

What was interesting, as I've said before, is when you break this data down by year, looking at 1996, '97, '98, you see what is, in fact, a very nice increase throughout those years. And, actually, as the line appears there, you can't see it real well, but it's a real nice regression line. In '96, it was 1 in 9,900; in '97, it was 1 in 7,200; and then in 1998 the rates had gone all the way up to 1 in 5,400.

Now, the simple explanation for why we see that increasing rate in Los Angeles was actually provided to us from the Southern California Region of the American Red Cross. During that same time, they had increasing efforts to include or to increase donations from the Latino blood donors and, in fact, as the populations change within our cities and all across our country, there is going to be a need to target the populations that are there in order to increase our numbers of blood

donations. In the case of Los Angeles because of the increasing numbers of Latino donors the blood drives were, of course, targeting the Latino population.

So what we see, not only in Los Angeles, but everywhere else, is as we see changing donor demographics, we are going to see enhanced minority recruitment efforts. These, in turn, are going to lead to greater numbers of at-risk donors being recruited, which then result in more seropositive donors which, in the end, leads to a greater risk of transfusion transmission. So this is something that's going to be a long-term issue not a short-term issue, as far as Chagas disease is concerned in the United States.

Now, when we talk about transfusion transmission, T-cruzi has all of the characteristics that's important. And I've heard some of these discussed this morning, that each agent needs to be evaluated on its characteristics, whether or not, as an emerging agent, it can actually be transfused. In the case of T-cruzi,

the stage is extracellular in the peripheral blood. It lives outside the red blood cells.

In some studies with our seropositive donors in Los Angeles, we were able to demonstrate that 63 percent of these seropositive donors were, in fact, parasitemic. So you can find parasites circulating in the peripheral blood. So already you have a risk factor or risk scenario for transmitting the infection.

What we also was found was this parasitemia was intermittent, and this is not surprising. Sometimes the parasites are present, sometimes they're not. And this will get into issues, and I'll talk about NAT screening a little bit later, when one takes a sample for this kind of study, a PCR study, the ability to detect parasites or the number of parasites is also influenced obviously by the sample size and the PCR technique one uses, but certainly they are intermittent.

We also know by our own studies and others that the parasite survives blood storage quite

well. This is another factor one has to consider--does it actually survive in stored blood products? It survives in platelets up to seven days. In red cells, we've seen it at least up to three weeks.

Published reports show at least five cases of transfusion-transmitted T-cruzi in the United States and two Canadian cases. What's interesting about these cases, the disease in each case was fulminate, and the recipients were, in fact, immunocompromised. So I've used the term, and I think it's quite appropriate in the past, that these are, in fact, the sentinel cases. These are the obvious cases, the ones that were easily detected.

There was also a relationship here with platelet products because, in each case, there was a platelet product involved, suggesting that platelets may, in fact, be the implicated product of choice, but then, again, because these are immunocompromised patients, they are more likely to get platelets. So there's kind of a give and take. But the point is that these people were

immunocompromised and probably very susceptible to

infection.

But probably more important and what we don't really have a handle on is what's happening in immunocompetent recipients. And these, these are the cases that likely are not recognized or misdiagnosed because they don't have any outward symptoms of disease or infection, and it's not something we're going to know about until years down the road.

Now, how would we deal with Chagas disease? Obviously, we're not doing anything in the United States at this time. There's a couple approaches that could be examined or implemented, and some of these have actually already been thought about. The most obvious one, and the one we always go to first, perhaps, is risk factor questions. One could use these for either outright deferral or selection of blood donors for some type of testing. However, we found these tests or questions, at least in our hands, as well as others have looked at these questions, and found them to really lack sensitivity There's also issues, when

you're talking about country of origin and birth, that these can actually be somewhat sensitive in nature as well.

Certainly, the possibility of product manipulation exists, pathogen activation. There have been studies published looking at T-cruzi, showing that pathogen activation is, in fact, feasible, but then again we've been hearing about pathogen activation for quite some time. We're still waiting.

Leukoreduction, there's been at least one study that I'm aware of that looked at leukoreduction filters for moving T-cruzi. It removed some, but not all. And in the case of T-cruzi, one parasite remaining is one too many.

There is also the talk, perhaps, of filtration studies. I haven't seen any published, using a filter of some sort to remove the parasite, but there again those are perhaps studies for the future.

What may perhaps be the more logical way to go would be some type of testing option. And

keep in mind that in virtually every country in North and South America, Central America, of course, included, there is testing in place for Trypanosoma cruzi Chagas disease, just not here in the States and in Canada. So the most likely approach, perhaps, would be serology. Individuals who are infected with T-cruzi have lifelong antibody titers that are relatively easily measured.

I've stated before, in these type of situations, that I really don't foresee a need for NAT testing for Trypanosoma cruzi. First of all, the individuals who have T-cruzi were likely infected as children either in their home country or through congenital transmission here in the States. So these are infections that are already well past the window period. There is relatively very rare cases of active transmission from the bug in the United States. So the usefulness of NAT that we've seen for West Nile Virus and for some of the other viral infections really doesn't probably apply in this case.

So, if you consider serologic testing, then it gets you to the idea of, well, what about selective universal screening? Some have quite eloquently proposed that why not just test individuals once, and if they are negative, they don't need to be retested because, presumably, they are not going to be infected here in the United States. But as we've looked at that issue more, trying to determine who and who should not be tested is probably much more complicated and would lead to more accidents and errors than just simply screening everyone.

I'll close with what I think, and this is my opinion, I think, not others, but what are the barriers or why is this, in essence, an unmet challenge?

I think, first, there is a lack of public and media awareness of exactly what Chagas disease, what it causes and particularly what are the issues surrounding it here in the United States. In fact, most physicians, if asked about Chagas disease, couldn't tell you too much about it at all. This

also applies to some of the other parasitic agents which we're dealing with.

In my experience over the last 10 years, as we've worked on Chagas and we have, in many instances worked towards what perhaps may one day be an intervention of some sort, we are constantly interrupted with new or, in this case, the latest emerging agent. So there is almost I would consider a preoccupation with the latest emerging agent. In some cases, it's very valid, certainly, with West Nile Virus, but in others we spend a lot of time talking about SARS for an agent that's likely not transmitted by blood transfusion.

Clearly, the biggest hurdle, perhaps, with Chagas disease has been the unavailability of a licensed and approved screening test. And I think part of that was from the trepidation of the manufacturers themselves to develop a test because they didn't know if it would be approved or if there would be a market for it out there. And I think, by and large, because of the FDA, at a September 2002 BPAC meeting, I think that hurdle

was eliminated when the FDA laid out quite clearly a regulatory pathway for donor screening. And at that meeting, I believe I have the quotations correct, they basically said that, if and when there is a test approved, that we will recommend blood screening.

So I think the manufacturers, and I am aware of a couple of manufacturers that are, in fact, working on test development. So, hopefully, there will be a test before too long.

And, lastly, and I've used this before, too, and I think there is a general ignorance of the parasite paradigm by and large because there is no parasite paradigm. We too frequently have fallen into the idea of using what we've learned about viruses and blood transfusion to apply to parasitic systems and maybe in some sense the bacteria as well.

When we're talking about Trypanosoma cruzi, there's relatively few organisms circulating in the peripheral blood. We're not talking about a viral that has logs, and logs, and logs of virus.

So some of the things we might consider or some of the things we might use, such as NAT testing, just don't apply, and that's just one example of many that applies to the parasitic systems that needs to be thought about as we talk not only about T-cruzi, but other emerging agents.

Thank you.

DR. EPSTEIN: Again, we're going to hold questions. Thank you very much, David.

So, next, I am pleased to invite Dr. Louis Katz, who is the Executive Vice President of the Mississippi Valley Regional Blood Center and also the current President of America's Blood Centers. Dr. Katz is going to describe HIV as a case example of evolving challenges, interventions and donor management.

Lou?

DR. KATZ: Thank you to the conveners for the invitation. It is with a little bit of trepidation that I address this particular subject. Some of you on the committee may not be aware that you exist as committee members on this committee as

a result of the IOM report that was a retrospective analysis of the events surrounding HIV.

This is a quote from MMWR that I'm guessing some of the grey eminences sitting at the table will recognize. This was from December of '82, platelet transfusion to a child that I think, at the time, was strongly suggestive and, subsequently, we all agree kind of clinched the transfusion transmission of HIV by whole blood and components. It concisely recognizes the features of the illness, asymptomatic carriage and a long incubation period to disease that made HIV such a challenge not only to our blood community, but to everybody in public health charged with its controls.

These are the major interventions that were discussed at a meeting of the representatives of the blood community and public health agencies responsible for transfusion safety in January of '83. Recall that all of the information that we had available at that time was epidemiological. HIV had not been isolated, and there were certainly

no validated tests to identify risk very well.

I'm happy to say that I was not at this meeting because I don't want to think about what my response would have been to the evidence as it existed at the time in the charged atmosphere that characterized the meeting, as I have interviewed people who were either there or were intimately familiar with the details of the meeting.

I had recently left the University of Iowa, where the infectious disease group that I was working with had been stricken by the epidemiologic similarities to hepatitis B and were asking questions about transfusion transmission actually substantially before this meeting.

These were specifically designed to reduce whatever risk was present, but I think there was not a consensus on risk to the blood supply. The latter, in yellow, was chosen, to the exclusion of the others, and it's probably reasonable to reconstruct, if we can, some of the reasons.

This slide may be considered provocative. I have talked to as many people that were there or

were close to the situation at the time, and I'm not going to vouch for the quantitative importance of any of these except the first. As I talked to people who were intimately involved in the first months, scientific uncertainty dominates every conversation that I have had, and then the other things are also listed.

Distrust of CDC I find to be an interesting discussion to have with people. We had not in the distant past been through the swine flue experience fiasco, as some would call it, and others in the blood community at the time tell me that there was some concern that budget cuts at CDC found CDC looking for a new cause. I will not vouch for the accuracy, and certainly not for the amount of distrust that might have existed.

The civil rights and ethical considerations I think are fairly straightforward, and I would only say that I'm an AIDS clinician from the beginning of the epidemic, and I am very sensitive to the rights of gay men and others that were identified at risk very early on. The fact

remains that gay men, Haitians, drug users and hemophiliacs were recognized by decent data to be at higher risk than others for what came to be known as Acquired Immune Deficiency Syndrome. With the heat of the moment gone, I think we need to remember that blood donation is not a right, it's a privilege, as is driving and other things that we do in this country and that alternative measures, in the face of epidemiologic evidence of risk and the absence of scientific certainty and alternative measures, we may have to, in the future, face similar allegations of discrimination and deal with them with a greater eye, perhaps, than we showed at the time to those who received the product that we produced--blood and components. I am not yet aware of a lobby from the primate workers about Simian Foamy Virus, but allegations of discrimination could be forthcoming at some point.

With the recognition of the putative transmission of the agent of AIDS, came one of the most concise statements I'm sure I've ever heard about the application of risk analysis to

decisionmaking. This is from Don Francis at that meeting in January, quoted by Shilts in his controversial book, "And the Band Played On."

"In the climate of the day, this was viewed by those of us in the blood community as somewhat hyperbolic. With the hindsight of more than 20 years now, it was clearly not so hyperbolic but, in any event, starkly highlights the calculus that we need to attend to with future agents."

Well, at the end of the day, this is just adults and adolescents who receive transfusable components. It's not pediatrics, and it's not derivative recipients, but it gives you an idea of what happened after we started to make decisions and begin intervention. And this is 9,000 cases through I think 2001.

It's interesting that, despite the intense focus on transfusion-associated AIDS, there remains no database that allows depiction of the epidemic as it should be depicted by date of transfusion. This is all by date of diagnosis. Display according to the date of transfusion might allow a

more precise understanding of the impact of the sequence of individual interventions that we applied to protect the blood supply. Water under the bridge, I suspect, but if Dr. Kuehnert can figure out a way to get a sampling with date of transfusion, I think it would be a more informative curve.

This is a quotation from the IOM report, "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking." And highlighted is I think that which made it most difficult for us--a new threat that was characterized by substantial uncertainty, and we have been found, by a few people at the time events were occurring, and pretty universally, in retrospect, to have been wanting.

By January of '93, we knew of, I believe, four cases in hemophiliacs, the case in the MMWR of a transfusion recipient and the similarity of the risk groups to those with a high risk of hepatitis B. This was strong epidemiologic evidence of parenteral transmission.

In the two-year interval before testing,

the certainty of parenteral transmission increased, and there were a number of opportunities to review our initial limited response, including three BPAC meetings in '83. But little was done as we accepted what we know to be a wildly optimistic and largely baseless estimate that the risk was "one in a million."

Missed opportunities included the opportunity to withdraw derivative lots, including plasma from infected donors, and to learn from local attempts to screen donors with methods that were rejected at the national level. Those include, as I've mentioned, Anticore and CD4-CD8 ratios.

The IOM found, and I quote, "Blood bank officials and federal authorities consistently chose the least-aggressive options that were justifiable. In adopting this limited approach, policymakers often passed over options that might--might--have initially slowed the spread of HIV."

Well, this is the chronology then of interventions, and the highlighted ones are the

ones that I think I identify as particularly of interest or instructive to this committee. I have already mentioned the initial events of 1983, and we'll show a little information that actually suggests that what was done initially might have been remarkably effective, which is not to say as effective as it could have been.

Serologic testing was started in March of 1985 and was, with all our issues of sensitivity and specificity, which we continue to deal with, in fact, clearly a watershed event.

The use of explicit questions about risk behaviors taught all of us, in the blood community, a very important lesson. Our donors are smarter than we are. When faced with a strong public health rationale for some incredibly intrusive personal questions, there was no important exodus of donors, which we had feared from the beginning. They proved themselves to be the altruists that we always accused them of being and continued to donate.

The implementation of NAT, under IND,

apart from its small quantitative effect on safety, represents a new paradigm for the blood community and the FDA, the use of an experimental test for mass screening of the blood supply, and I think we can congratulate ourselves on its application to West Nile Virus four years later.

The last is personal history. My blood center was granted a variance two weeks ago to allow us, on donors with a positive nucleic acid test, to stop using Western blot for confirmation, both for HIV and HCV.

Well, did it work, what we did? The highlighted area is when we were just asking people, if you're in these risk groups, please don't donate. And as you can see, the risk of transfusable components fell by orders of magnitude well before the agent was identified, well before serologic testing could be implemented. Again, that is not to say we were as effective as we could have been. This is a little of the same kind of data from Blood Centers of Pacific, Irwin Memorial Blood Center at that time, and it shows you some

quantitative data at one of the epicenters of the AIDS epidemic. It demonstrates withdrawal from the blood supply of infected donors, even as the number of potentially infectious donors increased exponentially in the Bay Area.

What is left? And just let me start by saying I made the same mistake Roger made and forgot about pathogen reduction, and so we could put that on at the bottom and nobody needs to ask.

Can we improve donor screening for risk? Probably. At my blood center, we use a multimedia interactive donor screening computer system and have demonstrated statistically significant increases in the rate at which our blood donors admit to high-risk behaviors, primarily MSM.

We can always use better specificity and sensitivity of our serologic assays. The improved availability of detectability of Group O in serologic assays would be nice. For those of us saddled with Company A, we still have to ask a bunch of questions about Africa that it would be nice to be able to remove.

It would be very nice to have improved specificity of supplemental assays for our repeat reactive donors with negative nucleic acid tests. We defer several dozen donors with a very, very sorry mixed message at my blood center every year with indeterminant Western blots. We know they're not infected, and the message, "Well, you're really okay, but don't come back to the blood center," is a very difficult message to give a blood donor.

Single-donation NAT is going to be an interesting discussion as the automated platforms develop that we require to do that and will stretch the limits of cost-benefit.

And then a kind of a rhetorical question, will there ever be sufficient confidence in serology and in NAT to adjust our deferrals for behavior? Most recently discussed at BPAC about two, three years ago. I thought the clear consensus of the committee was that if we believe that rescinding a deferral will increase risk based on even mathematical models, that we're probably not going to do it, at least during my lifetime, in

blood banking.

And this, I think, is where we've been left by the paradigm shifts that have occurred with the HIV epidemic. Classic public health perspectives in the blood arena is not relevant to either society or regulators. And I hope, by now, even we in the blood community have begun to abandon the classic paradigm.

Costs are apparently not relevant, and the move toward single-donation NAT for HIV and HCV I think is a good example of classic cost-benefit not being relevant to our arena.

And safety-based interventions that have been implemented, some of them based on little or no data, are difficult to rescind.

Recipient protection is paramount, and that should be in big letters and everything else in small letters. We need to develop the capability, as we apparently have with West Nile Virus, for rapid assessment, proactive decisions, often with inadequate data, and take action. Several people have commented on the globalization

of risk, so I won't dwell on it.

And, finally, my little plug. In a health care system that struggles to establish, and implement and react to priorities, we will continue to be guided by precautionism. And to anybody from CMS in the audience, at least we need to ask, and expect to be paid, for the safety.

I guess we're holding questions.

DR. EPSTEIN: Thank you very much, Lou. Quite a saga.

Our next speaker is Dr. Mike Cannon, who is an epidemiologist in CDC's Division of Viral and Rickettsial Diseases. Mike is going to talk about HHV-8, which we have put forward as a case example of an unresolved scientific question potentially affecting blood safety.

Thank you, Mike.

DR. CANNON: Thank you.

Human Herpes Virus 8 was discovered in 1994. It's an envelope DNA virus that's closely related to Epstein Bar Virus. And like other herpes viruses, upon primary infection, it will

establish latency and persist in the host. So that you have the potential for viremia long after primary infection occurred.

HHV-8 is primarily cell associated. And just some background on detection that will inform the rest of this presentation. Seropositivity often doesn't imply the presence of virus in the blood, and currently there are a variety of serologic assays and a variety of estimates of seroprevalence in blood donors that complicates things. And there is no FDA-approved serologic assay. HHV-8 is a necessary cause of Kaposi's Sarcoma and has strong links to other less-common diseases, primary effusion lymphoma and multicentric Castleman's disease.

And to give you an idea of your risk of disease associated with HHV-8, your risk of developing KS, and these numbers are rough estimates, it's about one in a million per year, overall, in the United States if you're healthy. Organ transplant recipients, there's a big difference right there. Your risk is 1 in 80,

annually. If you have HIV, it's 1 in 50, and if you have HIV, and you're known to be HHV-8 seropositive as well, you have a 1 in 20 annual risk of developing KS. So, while the risk is quite low overall in the general population, there are particular groups that the risk is actually quite high.

The first idea that HHV-8 may pose a risk to the blood supply came from a report that in a healthy North American blood donor this individual had infectious HHV-8 in multiple blood donations. Since then, there were a number of studies that showed HHV-8 to be associated with injection drug use as well hepatitis C virus infection, which is primarily associated with exposure to blood.

Sort of a next step is looking at, in blood donors, what is the prevalence of infection. And this slide comes from a multi-center study that was coordinated out of CDC and used specimens from the Retrovirus Epidemiology Donation Study, I believe. REDS is the acronym. And a couple points you can see from these different laboratories.

Each of the laboratories used one or more serologic assays, and they each had their own algorithm for deciding whether a specimen was seropositive or seronegative.

And you can see from that second column, the KS controls, all of the laboratories did very well at detecting the individuals who had Kaposi's sarcoma as being HHV-8 seropositive. But if you look at the column on the right, you can see that although the seroprevalence was in a fairly small band or small range, it did vary from half a percent to just over 5 percent, using statistical techniques, the best estimate of seroprevalence was 3.5 percent.

An important is that, in this study, PCR testing was done on peripheral blood and none of the 138 specimens that were tested had HHV-8 DNA, including 55 that were seropositive.

Getting to specific studies of transfusion transmission, just some highlights from the literature. There have been a couple studies done, and this is pretty much the total in the literature

that we have that looked at a total of 32 recipients of HHV-8 seropositive blood, and none of those recipients seroconverted. On the other hand, a more recent study done by the NIH showed that in Uganda HHV-8 seropositivity in children correlated with the number of blood transfusions they received.

Moving on to a couple of studies that CDC has played more of a primary role in. We did a study in Uganda, and this is an important place to look at HHV-8 transfusion transmission for two reasons: One, the seroprevalence in Africa, especially Uganda, is quite high, approaching perhaps 50 percent; and, second, that a lot of whole blood is transfused with short storage times. So, if transfusion transmission is occurring, we're likely to find it in a setting like this.

And the preliminary results, at this point an emphasis on "preliminary"--they're unpublished--but it looks like the group exposed to HHV-8 seropositive blood was about twice as likely to seroconvert, and because of the numbers, this was a

statistically significant difference.

Another relevant study is from the FACT Study, which is a U.S. study based in the 1980s, and it was specimens from individuals who had cardiac surgery, most of whom received transfusions. And the major limitation of this study was that although it did have pre- and post-transfusion specimens from the recipients, there was no donor link.

And what we found in a paper that's to appear in transfusion was that 2 out of 284 HHV-8 seronegative recipients seroconverted, representing a .082-percent transfusion risk per transfused component. And this is roughly one-fifth of the transfusion risk of hepatitis C prior to HCV antibody screening.

Now, what does this mean? This is really the only study in the U.S. so far that has shown evidence of transfusion transmission. The caveat is we can't definitively say that this infection was transfusion acquired, one, because of the lack of statistical power to do so and also because of

the lack of corroborating evidence from donors. But we do know that there were no seroconverters in the nontransfused group. These were men in their sixties, and community-acquired infection in the U.S. is unlikely for them, and they each received, they received 12 and 13 transfused units. So it was consistent with transfusion transmission.

Now, it's important to recognize that this rate of transfusion transmission is likely to represent an upper bound. Since that study was done, the donor requirements are much more stringent, and there's laboratory testing done for agents such as HCV that do share some risk factors with HHV-8. Furthermore, leukoreduction eliminates most white blood cells which are the presumed reservoir for HHV-8 in blood.

Finally, moving on to where do we go from here. It's very clear from the literature that the HHV-8 serologic assays perform quite well in epidemiologic studies, very consistent across laboratories and populations. However, diagnosis of individuals is much more difficult, for several

reasons:

One, the true seroprevalence is relatively low, so you've got to have highly sensitive or you have to have highly specific sero assays, but an interesting fact about HHV-8 is that, if you recall from that slide from the blood donor study, all of the laboratories agreed on the positive KS controls. But it turns out that if you look at individuals who are in a low-risk category, low risk for developing KS, such as blood donors, but you have corroborating evidence, perhaps multiple assays or longitudinal follow-up, so if you take these low-risk individuals who seem to be truly infected, their antibody, the sero reactivity is quite low, is quite weak. So you need very sensitive assays.

In general, what is needed for resolving this scientific evidence is continuing collaborative efforts. And this has been a hallmark of a number of several studies in HHV-8 and blood safety that have included academic and industry collaborators, along with NIH and CDC and,

additionally, a determination whether or not this should be a priority. And that depends on, for one thing, we've learned from these recent CDC studies that it's possible that there's HHV-8 transfusion transmission,b ut in light of that, we also recognize that for most recipient groups, any risk of disease, even if they become infected through transfusion, is quite low. Nevertheless, these initial studies seem to indicate that we can't say at this point that there's a nonzero risk of getting HHV-8 through a blood transfusion and subsequently developing disease.

Specific steps to take at this point are to more precisely determine the risk of HHV-8 transfusion transmission if it, in fact, occurs. One thing we're working on with collaborators is a donor recipient repository from the 1970s where, if there is HHV-8 transfusion transmission in the U.S., it's most likely to be detected in this sort of study, which has the advantage of having linked donor recipient specimens, and that's a study whose results should appear quite soon.

But we also need studies of current linked donor-recipient repositories. An additional study that's a logical step would be to study the effect of leukoreduction just in the laboratory on HHV-8 viral load to see whether, in fact, or how successful it is at reducing viral load.

Additional studies, such as modeling the cost benefits and the potential disease burden, are logical next steps, and then given if these steps indicate that donor screening might be appropriate, assays, of course, need to be developed to have the high sensitivity and specificity and, in addition, high throughput capability. And the difficult part there is that in the blood donor study and in other studies, we've seen that the most sensitive HHV-8 sero assays, for the most part, have been IFAs, which don't have the high throughput capacity that would be necessary.

Thank you.

DR. EPSTEIN: Thank you very much, Mike.

So the last presentation in this case series will be by Mr. Mark Skinner who, in addition

to being an Advisory Committee member, is the current President of the World Federation of Hemophilia. And we've asked Mark to discuss variant CJD, primarily from the perspective of risk communication.

MR. SKINNER: Good afternoon. This actually builds on several presentations that we've heard, most notably when Shannon was speaking about the work of the consumer organizations. I want to pick up on a couple examples that she was speaking about in relation to variant CJD. I don't really need to talk about this. It really all starts with the premise that variant CJD is transmissible in blood. These are the two relevant published articles on that.

The question then became what do we do once we know it's transmissible in blood. The second individual who was diagnosed with variant CJD was, in fact, a plasma donor or a blood donor. And through the records, then, we identified that, in fact, his blood was used in what you see on the screen, the batches of Factor VIII, Factor IX,

albumin, antithrombin, IGIV, and then also it was used in Cryopaste, then, which was further sold to the Netherlands for fractionation. And then more recently we've learned that his donation was actually commingled with plasma from Belgium that was used in contract fractionation. And then there were, also, part of his donation was actually used by the Scottish fractionation company, PFC, as well.

So the question then became what is the risk for those that are users of the plasma products. This, in fact, is the statement from the U.K. risk assessment that basically indicated that not only those individuals that received product from donors later known to have variant CJD, but, in fact, the entire population, 6,000 individuals in the U.K., were identified to be at risk for variant CJD.

This is more complicated than you need to see. It's simply to indicate that the U.K. established a very complicated and full and comprehensive notification system through the

public health agencies and to the patients, in terms of how they were going to deal with the response. So what's relevant to this committee, really, is what are the implications for residents outside the U.K., and what I've tried to put up here was a time frame in terms of what they occurred.

If you think back to the first slide, where I indicated that on September 7th was when BPL and PFC identified the implicated lots and products and announced them, the U.K. Hemophilia Treatment Center directors were actually notified, but the information was actually press embargoed on September 9th. The World Federation, through its contacts, actually, received notification in this intervening period, but the U.K. did not actually notify it publicly until September 21st.

The WFH, then, initiated inquiries to BPL and PFC to actually inquire as to the lot numbers and to the distribution and the exportation of the products that they manufactured. BPL and PFC declined to provide that information. In fact, NHF

in the U.S. actually sent a formal letter of inquiry as well, which, to date, has actually not been responded to.

Then, the World Federation, through its own global data collection, through our global registry and through our tracking of where products are used in the world, began to receive patient reports on countries in which BPL products were distributed, and the number varies anywhere from 6 to 10. But, in fact, none of these countries ever received notification through the official chains to the patient users or through the distribution systems within those countries. We have some reports that the embassies of those governments were actually notified in London, but obviously that's nota particularly efficient way of communicating the information to the end user.

Then, the U.S. became actually directly involved in September 22nd, when we had an individual, a patient with Factor XI, in the U.S. who self-reported to the World Federation of Hemophilia, inquired about the information that she

had read in the press the day before. The World Federation then, obviously, notified the U.S. and myself--I mean, I was in that loop--and then we contacted the FDA to inform them that we had information that there was, in fact, a compassionate use trial in the U.S. for Factor XI manufactured by BPL during the time period in which the products were collected.

There, in fact, was not a specific donor with vCJD that contributed to the donor pool for those Factor XI patients, but if you keep in mind that all patients in the U.K., regardless of whether or not they received product, were now told that they were at risk for variant CJD. We contacted the FDA to inquire about what steps the FDA was going to take at that point. We have since learned that there's probably somewhere less than 100 patients in the U.S. that did receive BPL product, and the FDA is in the process of establishing its own risk assessment, which may well be different than the risk assessment that the U.K. established.

The NHF, then, as the patient representative organization of the community, was left with little choice. In the absence of guidance from our own government and in the absence of a response to our inquiry to the U.K. fractionation companies, NHF issued a medical advisory to the Hemophilia Treatment Center directors in the U.S. indicating that there was the potential that some of their patients had received product from U.K.-sourced plasma and informed them what the notification process was and what the recommendations were in the U.K. for those patients. And that is the guidance that is sitting out there today in the Hemophilia Treatment Center network.

There have since been risk assessments from other governments in Canada, in Belgium, in France, all of which are slightly different, and I understand there's a mechanism coming towards the end of the month where the countries are going to attempt to reconcile that. And, in fact, the BPAC meeting I think will be taking up that topic on

February 8th.

The next example that I want to talk about is variant CJD in France. In fact, this just occurred, if you look at the bottom of the slide, you'll see January 13th is when we received notice. So this is a very recent example of another gap in the communication chain.

The eighth case of variant CJD in France was identified on the 21st of October in 2004. The donor's plasma was collected by LFB in this example, and it was later acquired by Centeon as Cryopaste. In fact, the plasma, though, the Cryopaste actually was not received directly from LFB. It was actually received in the distribution chain as Cryopaste, where it can be sold and then resold and then was ultimately acquired by Centeon.

The troubling part about this is that ZLB initiated a voluntary look-back, which they should be congratulated for. They did that for the eighth case, as well as the ninth, and then all of the antecedent cases, but nowhere during this time was ZLB ever notified that they had actually received

Cryopaste containing donations from a donor that was later known to have variant CJD. So there is a distinct gap in the way the notification process has occurred in France with LFB to perhaps the end users or the recipients of the plasma products as they're further distributed.

What LFB did do, to their credit, which BPL did not do, is that they actually had published their lot numbers and actually contacted those that they know that received products from one of the implicated lots for product made by LFB, but they haven't gone the next step to talk about down the chain where their intermediates might have gone for further fractionation. And then the patient community was informed by ZLB on the 13th of January, and then subsequently the relevant patient organizations were further notified.

So this is the second example of a different gap, but it's a variation on a theme, in terms of notification, and particularly in a global context as it can relate to patients outside of the country of origin.

So this is just a list as we know it today of the fractionation companies in the world that, in fact, have processed or received product known to have contained a donation or processed products that have contained donations from donors that were later known to have variant CJD. You can see the spread across Europe. And if you know or have a general sense of what products are made by these companies, you'll know that many of the products for the patients with rare bleeding disorders are, in fact, made by these companies--Factor XI, Factor XIII, Factor V, and some other products which are not made or currently available in the U.S.

Here is a list of just the implicated products as we now know them. Again, all of these products did not necessarily contain donations from an individual later known to have had variant CJD, but at least they are on the list for one reason or another--because the U.K. government put them there or because they are known to be specifically implicated.

So my comment here, and as they relate to

those of us sitting here in the U.S., is we do know that migration of product in plasma occurs around the world. It's a little bit different than blood, that plasma can be bought and resold and that there is a market for plasma among the fractionation companies.

Just to summarize the two examples. The first example was a gap in communication to the patients and to the end user outside the country. The second is a gap in notification or communication within actually the production chain. All of this really originates from our basic premise that the patients do have a right to be informed, but there clearly needs to be a balance in terms of that patient information and how that goes about.

The U.K. system because it was so aggressive and because, in fact, the guidance that I didn't go into was so far reaching that we're now seeing an access-to-care issue in the U.K. Dentists are refusing to treat patients with hemophilia. Patients are being denied access to

procedures that require an endoscope or a colonoscopy because of the inability to have certainty that the equipment can be sterilized subsequently. So, certainly, we have a concern that if those procedures are carried forward and how that risk is communicated to patients, that that would not translate to the Factor XI patients here in the U.S.

The other issue that I wanted to point out here is the patients in the U.K. were not notified for their own personal health. They were notified as a mechanism to prevent a secondary epidemic in the broader public health through the risk of secondary transmission from one of those types of instruments or medical procedure. So you have a large group of patients that were stigmatized and are at risk of access to care, and we're certainly working to address that. And so the countervailing argument to that is you could certainly underreact and have a lack of transparency to the system then where the patients don't know.

So there is a very careful balance, and

that really goes to what the balance of the comments are; that it's certainly very important, and this goes to the globalization of regulation, that foreigners and nationals are treated equally in the process and that we're particularly attune to that as we think about plasma-derived products, that counseling and competent explanation is required.

And I should point out here that the U.K. Hemophilia Treatment Center directors were never informed, never consulted. They were simply handed a letter by the government and said you will, without exception, send this letter to all patients in the hemophilia community in the U.K.

And so the direct application to this, I think as it continues today, really is those patients that we talked about at the last Advisory Committee meeting and then yesterday morning here, is the patients with rare bleeding disorders that might be dependent upon products from one of these companies, either on a compassionate use basis or that might come in through an investigational IND,

where they might be sourced from a U.K. or a non-U.S.-sourced plasma. I know there's regulations that would have prohibited that in some instances going forward, but we don't know exactly now where the products have gone and where the paste has been used.

The other outstanding question is ZLB has taken the initiative to do it, I'm not saying that the other companies haven't, but we don't know what the other companies now have done that might have purchased Cryopaste in the open market and used it in the fractionation of their products.

DR. EPSTEIN: Thank you, Mark.

So, Mr. Chairman, that concludes this panel of presentations of what we called case examples that are agent specific, but that were intended to illuminate different dimensions of the system's response to the challenge of emerging agents or newly recognized risks.

DR. BRECHER: Thank you, Dr. Epstein and to all of the presenters. It is very illuminating and somewhat frightening.

We're going to move into the Public Comment section. I'll ask anyone who has public comments to come up to the microphone, identify who they are, what company or organization they represent, and please keep your comments to five minutes or less.

MR. DUBIN: Corey Dubin with the Committee of Ten Thousand.

It was rather sobering to listen to Dr. Katz, who chaired the BPAC when I first came in, asking myself what I had gotten myself into. But thanks to Dr. Katz, I progressed well. And it was sobering. And I'm going to remind you of some of the things I reminded you of yesterday.

There's a lot of dead bodies around when I listen to Dr. Katz talk or I listen to Roger Dodd or others that I've known through the process. I think one of the things that we pride ourselves on is, as the Committee of Ten Thousand, as people with hemophilia, HIV, and hepatitis C, and that is really our constituency, we see ourselves as part of a larger disease community that reaches outside

of hemophilia. We see ourselves, in part, as citizens of part of the chronic disease community in this nation, and we want to always remind ourselves of that because it's rather easy to get insular about one's own condition and one's own disease.

I have the advantage of having a view all the way through this epidemic, from beginning to the present, and some things really come to mind as I've been talking to people over the last two days. HCV look-back and the question of hepatitis C, Greg Haas, Tom Fahey, myself and Jonathan Wadleigh raised HCV look-back with successive FDA Commissioners starting with Kessler and starting in 1994. And there really has never been serious action on HCV. There was some money that went to CDC. There was supposed to be a public media campaign. I've seen one of those on a bus on Chicago. It's the only one I've ever seen. I heard rumors there was one up on the Metro in D.C. Nothing has ever been done.

And when I heard some of the priorities

listed today, I'm not sure I heard very much about hepatitis C, only we have a huge epidemic out there that we're doing nothing about, it seems to me, and that's a policy issue, it seems to me, that cries out for leadership from HHS. And that's just one Fund them. CJD, we're still talking about CJD and variant CJD. I think what's lacking for us is coordination between food and drugs. The two sides of the FDA, in our mind, aren't communicating well enough because the connection between food and donors and food in the blood supply, as far as we're concerned, is not a priority enough that actions are happening in tandem or in coordinated efforts that probably should involve the CDC as well.

We have entered a period when I think it is most important for us to prioritize limited resources. I don't think we're going to get any big budget increases for any of the agencies I've spoken about, but one thing is interesting to note. I heard the word "postmarket surveillance." We raised that with Commissioner Hanney, in believe,

1994 or 1995.

If we want to seriously look at postmarket surveillance, which many of us believe is an absolute necessary piece of the puzzle that's not occurring, just look in the news today, look at Senator Grassley's investigation in Vioxx and others. You've got to give the Agency the resources to do it. FDA, as it's currently structured, couldn't possibly undertake the level of postmarket surveillance. I think it's thrown around in discussions. It's not something to be taken lightly. And if it is a priority, then we need to get to work with Congress so they understand what resources are necessary so we're not asking the Agency to do something that they can't do.

As I said to Jay, I'm one of the people that's been very critical of the Agency at times, but at the same time,it does not help to throw criticism when there's not staff or budget to do a job that needs to be done.

This committee was all of our hope, all of

us who pushed for the IOM and worked on the early structuring of this committee, that this committee would be the interagency push or the interagency coordination. I think, in some ways, that's happened, and I think that's begun to happen, but I think there's some critical issues we continue to sidestep or maybe sidestep is too strong a word. I'm not sure, but I know when I'm still standing at a microphone in 2005 asking about hepatitis C and talking about a hepatitis C look-back that never happened, something is wrong. Something is not getting through correctly. The size of the hepatitis C epidemic will probably dwarf HIV when it's all said and done, and we're really not doing anything.

There are a lot of things that need better coordination, really cry out for it, and I think there are hard things that we need to get to the business of really looking at and coordinating it. And I think if we want to prioritize some of these things, then we have to take it to another level. We have to do some outreach, as I said earlier on

the Hill, and we have to do some outreach in the society because much of the debate that goes on here doesn't get outside.

It has very little legs in the public at large, but I think it needs to. It's important. If it's important enough to bring everybody here and capture everybody's attention and all of this time and effort, it's important enough to take it to the public, and it's important enough to think about how to structure the message because I've heard a lot about controlling the message, and this is always something where the Committee of Ten Thousand and the NHF have differed--the message.

First of all, you're not the only representative of the people, Mark, and it's time to stop saying that. There are multiple organizations, and it's important to be inclusive. This committee was established to be an inclusive body, and I think it needs to continue to be. And we all need to understand that everybody has a role to play. Excuse the break in my voice, but watching these slides and some of this goes on is,

again, quite sobering to look back.

We still haven't done some of the things we need to do. And so I would urge the Committee to step back and look at some of those links that need to be established in between FDA and CDC, in between FDA itself and maybe do some work with Congress to understand what FDA really needs to do its job.

I think those are some of the things that some of the groups that speak before you and come before you can spend a lot of time working with all of you to make a better presentation and get it to the public and get the issues on the table.

The last thing I want to say is we, at the Committee of Ten Thousand, continue to be very worried about CJD and variant CJD, and we want to keep that on the agenda. We don't want to see that swept aside. We've heard the British overreacted. We're not sure about that yet. We're still doing our own investigation with people that we have on the ground in Great Britain and the community. We'll have more to say about that.

I do want to thank everybody for the hard work. I think that doesn't get done either, and it's important, but there's a lot more to do, and we really need to get to work because I hear a certain level of, in closing I want to say, I almost hear a certain level of, "That's what happened in '82 and '83, but we feel pretty comfortable that nothing like that is going to happen again." That's not something I want to hear because I don't think it's true.

I don't think it's a question of if it will be; I think it's a question of when it will be, and what will it be, and will we be ready to respond. And I think this committee is critical to any future response because this is where the different agencies come together.

Thank you.

DR. BRECHER: Thank you.

Additional public comment?

MR. BAKER: I want to thank the Committee for giving me a brief opportunity to share some information with you that I think is important to

discuss today. My name is Hal Baker. I'm the Senior Vice President of Global Marketing and New Product Commercialization for Pall Medical.

We're about to introduce an exciting new filter in Europe this spring that can remove infectious prions from red cell concentrates using leukoreduction technology. I wanted to make the Committee aware of that. Because of time restrictions I will keep my comments brief, but I hope that there will be an opportunity in the future for the Committee to consider giving our principal scientists an opportunity to come forward and share much more of the detailed research behind this technology.

As most people here are aware, in North America and Europe, several measures are currently used to reduce the risk of transmission of variant CJD. They include geographic residency restrictions in the form of travel deferral and bans on importation of beef from BSE countries. In addition to these preemptive measures, many countries have implemented universal leukoreduction

as a precautionary principle because we know that up to 40 percent of pathogenic prions are found in donor leukocytes.

Animal studies have demonstrated that the agent that causes the human form of mad cow disease can be transmitted through blood transfusion. And with recent news from the United Kingdom confirming that a patient received donor blood through an operation in 1997, developed variant CJD and died six years later, transfusion medical professionals and the general public do now perceive the risk of developing vCJD from a blood transfusion may be a growing, not a declining, threat to patient safety. The existence of asymptomatic prion carriers raises real concerns of a second wave of transmission.

Are thousands of dormant carriers of vCJD at risk of developing clinical disease? These fears are supported by recent scientific findings. One of the two cases involving preclinical vCJD in the U.K. was detected in a patient who was heterozygous, methionine valine or MV at Code 129 of the prion gene. This finding suggests that

susceptibility to vCJD infection is not limited to the homozygous or methionine methionine, MM, genotype. The combination of the MM and the MV genotypes comprise approximately 90 percent of the U.K. population.

I think it is fair or safe to say that in the last several years a safety paradigm of sorts has emerged. Maybe a blood tripod might be one way to describe it. Using donor screening and selection, an increased reliance on blood screening tests for pathogens and the search for a variety of new safety processes, pathogen inactivation may be one good example of this Holy Grail.

Paraphrasing Roger Dodd and his editorial in Transfusion earlier in the year, donor deferral policies have a reverberating impact on blood availability as each future generation is lost. One percent of donors involves approximately 75- to 80,000 individuals in the first year not to mention their future potential donation. So it certainly is one measure. It has its consequences.

Those who are concerned about blood safety

would like to improve the sensitivity of current methods designed to protect against transfusion-transmitted infections. Those who are concerned about blood availability would welcome standard methodologies to detect infectious prions in blood. Such solutions are easy to think about, but hard to achieve.

The causative agent for BSE and vCJD lacks nucleic acid and therefore cannot be detected or inactivated by existing procedures targeting nucleic acid components of the pathogen. And any new prion test, regardless of its makeup, comes with a significant price of its own--the potential impact on donors who are subjected to it.

We're going to take a little bit different approach. And we believe that filtration, smart filter technology, can be the third leg of that safety tripod. So our approach to improving safety of the global blood supply grows out of our core competency and material science engineering and a legacy of leadership in blood filtration technology. It's natural that our solution

involves a novel proprietary surface modification technology that removes all types of prions, including normal and abnormal.

This new filter, the Leukotrap Affinity prion reduction filter is going to be introduced, CE-marked for European market sale in the spring of this year. We know that leukoreduction, as it currently stands, is a necessary but, by itself, insufficient to tackle the TSE infectivity that is not so associated; hence, the reason for bringing this new capability forward.

The filter's innovative technology is designed to provide dual benefit of reducing leukocytes below the level of the European guidelines and infectious prions below the level of detection of the Western Blot Assay in a single step. So this includes prion infectivity and blood that resides in leukocytes and also in plasma that's not cell associated. We believe the advantages of this type of targeted removal filtration as a safety process may be compelling as a more cost effective measure than adding an

additional step or a new procedure to the safety tripod that isn't currently used, maybe more efficacious than technologies that add new chemicals or new solutions that haven't been used in the past to blood, and it can be a widely applicable process, easily scalable and efficiently integrated with current blood handling logistics and good manufacturing practices.

So I won't go through the rest of the presentation. I have provided some material to the Committee that gives you an overview of some of the test methods that we've used to validate this prion reduction process, both exogenous in vitro spiking tests, endogenous infectivity studies, bioassay, all the tools that are currently available for validating the removal of prions. At the same time we've conducted an extensive battery of studies demonstrating the safety and efficacy of the filter for us with packed red cells for transfusion. U.K. National Blood Service has already confirmed that they will begin to use this in a Phase I validation beginning in the spring as soon as the product's CE

marked.

So if it pleases the Committee at some point in time in the future, we'd be happy to go through this in much more detail and present a lot of the science and a lot of the work that's already been done behind this technology.

Thanks for your time today.

DR. BRECHER: Thank you.

Any other public comments?

[No response.]

DR. BRECHER: We're a little behind. We have a lot to do, and some of our members are going to disappear on us, so I'm going to suggest that we skip the break, we keep moving. If you have to take a little break, disappear for a few minutes, but we're going to keep going.

Next on our agenda is Dr. Holmberg is going to give us a Structured Policy Processes; Framework and Principles: Review of Overseas Development and Institute's paper.

I'm sorry. I skipped the panel discussion. I was a little behind. Let's do a

short panel discussion, let everyone have an opportunity to ask the speakers who are represented in the panel, and let's try to limit this to 15 or 20 minutes.

So the panel members, maybe they want to come up so we can include them in this discussion. They have some microphones set up at the table here.

DR. HOLMBERG: Mr. Chair, would it be advantageous to try to capture some of the positive things and some of the gaps as we go through this?

DR. BRECHER: Yes. If we could maybe get that up on screen, that would be good. What did we do right? What did we do wrong? What can we do to avoid making mistakes in the future? I think that should be the theme of this discussion.

DR. HEATON: I've got one observation that I would like to make, and that is I noted that in the report on the plasma sector, there appeared to be very little in the way of harmonization of follow-up and look-back procedures. You know, you saw evidence of international traffic in blood

components or subcomponents of fractionated product, and yet there was really no consistent approach to providing certification to the next vendor. You know, in divided manufacturing you usually do have an obligation to follow up, and yet each country to pursue strictly national interests. So I believe one of the issues that we might want to consider would be some forum to develop harmonized notification requirements in the event of post-donation information becoming available to plasma fractionated products.

DR. BRECHER: It would seem there was also a lack of tracking some of these products. Maybe we could do a better job tracking these products.

Chris?

MR. HEALEY: I think Andy's comments are well taken, and I appreciated Mark's comments as well.

Just a little bit of background. I think it's important to understand any intermediates that are used for fractionation in the U.S. have to be collected from donors at licensed plasma collection

facilities, licensed by FDA. It sounds like in this circumstance it was a product that was manufactured probably from marketing abroad and brought in under a humanitarian use exemption or an IND or something of that sort. I do also want to let you know that PPTA has a standard for intermediates for its member companies, for any company that wishes to adhere to it, where many of the attributes that Andy was mentioning are actually in place, so there are tracking, recordkeeping, documentation requirements that must travel and consistent with chain of custody for intermediates that are distributed from company to company, as well as a maximum number of those transactions. So I believe it's three. I'd want to go back and be certain about that, but I believe there can be no more than three exchanges of an intermediate from producer to producer.

Now, of course, that's not universally accepted. That's a PPTA standard that's available for anyone, and it doesn't necessarily solve the problem of particularly a national fractionator,

when they discover a problem, pushing that information out to its customers, and I think that's really where the challenges is, rather than doing the great job that ZOB did, a retrospective, a look-back, instead pushing it out forward with the material once that information is gained. And so I think that's part of the point there.

DR. SKINNER: I concur with everything that Chris said. I really think the issue is for the U.S. patient population are the rare blood disorder products for the patients who don't have access or for which there are not products currently licensed in the U.S. And those products are going to continue to come into the U.S., and what ability we have to leverage the governments or those foreign manufacturers may be limited, but we should at least recognize that there's a gap in the communication chain and notification process that's not consistent, and figure out a way to manage back if we don't have the ability to leverage them proactively in the advance to adhere.

I do think it is primarily the domestic

fractionators, but in fact, they're the ones, because they had the country mandates, that actually they could afford to produce these rare fractions that are expensive for the others to produce. So it's a very difficult problem when it deals with international regulation.

DR. HOLMBERG: Concerning the Chagas disease and also the HHV-8, it appeared that there was a common thread there, and that is in the testing capability. With the HHV-8, if I remember correctly, you were saying that you really need a increased sensitivity in the testing. And with the Chagas disease it's basically that there's nothing, there's really no commercial test available. Is that correct?

DR. LEIBY: As far as Chagas, that's correct. There's no licensed test in the United States. I mean certainly there are tests used throughout Latin America for blood screening, but those tests are not approved for use in the United States.

DR. BRECHER: Just a quick scientific

question. You said much of the transmission probably in the United States of Chagas disease is vertical, congenital. When you acquire Chagas disease in infancy like that, do you form an antibody to it?

DR. LEIBY: In fact, yes, you do, and that's a problem in determining who, at least in endemic countries, who acquired infection through congenital infection or natural transmission. But that's right, you do get an antibody response. That said, they have an antibody response, but they're also likely parastemic, so they still are capable of transmitting infection.

DR. KATZ: I just want to point something out about the availability of lack of availability of tests, and just I'm preaching to the choir probably, but I have to say it out loud and in public, is there has to be a market before the tests are developed. There has to be some level of certainty at the point of those who are going to make these kits, that they're going to sell these kits, and we shouldn't--I mean to create that

market requires explicit priority setting well in advance of the availability of the test.

DR. BRECHER: Celso, then Jay.

DR. BIANCO: Just to clarify something that Mark said, the impression became that the biggest source of transmission of Chagas in the states is vertical transmission. Is that all documented? I think that that stayed in the air.

DR. LEIBY: Transmission?

DR. BIANCO: Yeah.

DR. LEIBY: I mean there's only been--there's been five cases of vector borne transmission in the United States.

DR. BIANCO: No, but I'm saying vertical.

DR. LEIBY: Right. I'm going there, Celso, if you give me a chance. There's been five cases of vector borne transmission. Now, if the transmission rate thought to be vertically is anywhere between 2 and 11 percent in a seropositive mother--this is based on the Latin American literature--then certainly there would be more cases of vertical transmission in the U.S. than

natural transmission.

DR. BIANCO: This assumption is not based on epidemiological data acquired in the United States.

DR. LEIBY: Are you suggesting that the Latin American literature is not a good source to base our--I mean, I would be glad to do a study on vertical transmission in the United States if someone's willing to fund it. The point is, these studies have been done in Latin America, the data is there. And this goes back to the point of looking at data that exists and saying that it's not important, it's not real. The same thing people ask, is there transmission, blood transfusion of Chagas in the United States. There's plenty of examples throughout Latin America that transmission by transfusion occurs. I don't care if we even show it by look-back or not. We know it occurs here.

DR. BIANCO: I think that the issues that we are trying to discuss here is different, and that's I think where we are seeing help, that is,

how do we do things right, and how do we prioritize what we do? That is, I think that we will have to place Chagas in the list of all the other priorities that we have, and how do we address them? And I think that that's at least what I see the role of this session in the Committee today.

And I want you to help not just with Chagas, David, but with the other parasitic diseases that Roger reviewed. And a big example is malaria that leads to a very big donor loss, and we have no resources, no assays like for Chagas, and how much effort you put in one, you put in the other one.

DR. EPSTEIN: I want to come back to a parenthetical remark that Roger Dodd made, which was that there appeared to be different levels of response or action to different agents or threats despite comparable levels of evidence of risk. And I think that that gets to the heart of the question of what determines the sense of urgency and what determines the public health priority? And I just wonder from the standpoint of the different

etiological agents that you've commented upon, what you think the key determinants have been in response or non-response? And I understand that there are many dimensions to consider but what do you think looms large in what governed how we reacted?

MR. : You're setting us up, Jay.

Well, I'm so badly conflicted in this. I have said for years, give me some of the money we spend on nucleic acid testing for AIDS drug assistance programs, and I'll prevent some bad outcomes. At the end of the day it's bad outcomes that we're trying to prevent. The problem is that we're making decisions before--we have to make some of the decisions before we know the magnitude of the bad outcomes well into the future, and I think the MV heterozygote vCJD transmission, is a great example of now we have to deal with this new input, and we're all pretty sure that if clinical disease is going to occur in MV heterozygotes it's going to be with a longer incubation period. How do we decide now?

At the end of the day it's prevent the most bad outcomes that we can prevent, and we have to make those decisions in a data vacuum frequently.

DR. SKINNER: It's probably one of the truisms that we've heard before at this Committee, is that a unknown risk is more frightening than a known risk, drives those decisions.

DR. BRECHER: Ed, did you want to comment? And then we'll come back to--

DR. TABOR: Well, I was going to come back to something that Dr. Katz said about three or four minutes ago. Maybe I should wait till they finish answering this one.

DR. BRECHER: Okay. Mark?

DR. SKINNER: I guess what I was going to say is, I mean, for those that are dependent upon a product at the end of the chain, I mean in terms of the plasma products, unfortunately we're always going to be looking in retrospect for our products. I mean if a problem shows up at the end in the plasma users community--and I think our goal is to

focus on evidence, but the problem's going to be fixed more by focusing on how we can find a mechanism to increase the robustness of the fractionation process, and that was what I was really going to earlier, is understanding what is transmissible. And focusing our energies there might be better than always trying to look back from the end. And I mean anticipating that there needs to be a broad spectrum of inactivation, as opposed to trying to prioritize it agent by agent.

DR. BIANCO: Jay, just adding to your question, I think that Roger tried to answer it when he put the two axes, one of them being public perception. So public perception has driven CJD to the height of perception despite the number of cases, when we just heard that HCV, that is much more prevalent and has many more bad outcomes, seems not to have reached that level of perception in a population.

DR. BRECHER: Ed, do you want to go?

DR. TABOR: Yes. A few minutes ago, Dr. Katz said that the companies will not work to

develop assays, at least not work at an advanced stage of development, until there's some sort of assuredness that the assays will be needed and that the investment will be paid back. And an example of where that was to some extent not a problem was West Nile virus, although even then there were discussions during the course of the development about whether it was actually going to be used after it was developed.

At the other end of the spectrum are diseases like HHV-8 and Chagas, where perhaps for a variety of reasons, but at least partly, certainly people are not sure yet that any effort to develop tests is going to pay back. As a result, the research ends up being done largely by government laboratories, or perhaps also laboratories like the Red Cross. Safety often comes down--the investigation of safety issues often comes down to a government responsibility because it's not something people want to take on as a proprietary responsibility.

But that said, many of these studies, for

instance, the studies described by Dr. Cannon, are being done out of research budgets that are the routine operating research budgets of these laboratories. There's very little room for flexibility in these laboratories, and there are many studies that could answer some of these questions that don't get funded or are not done because there are no extra funds. And the administrators in these agencies don't have the flexibility to put funds behind the priorities.

And I think the HHV-8 is on here as an example, perhaps as a case in point of something where we know what the questions are but we haven't got the answers are but we haven't got the answers yet, and before we go to those answers, we won't be able to get attention for the problems.

So I think one of the things to consider in the discussion here is--I know you're already considering how you set priorities, but then in addition, how can you find ways that these parties can be funded outside of what amount to unfunded mandates.

DR. BRECHER: I think in the interest of time, we do have to move on, so Jerry is going to give us an abbreviated version of his presentation.

DR. HOLMBERG: Thank you.

The title of the talk here is "Structured Policy Making on Blood Safety Framework and Principles." And really, I owe a lot of the material here from Julius Court, from the Overseas Development Institute in London. Julius was hired by the World Health Organization to develop a background paper on blood policy. And also I'm going to use some information that I have gleaned from the draft "Good Policy Process for Blood Safety and Availability" from the WHO.

One of the problems that we have with policy and writing policy and evaluating policy is that usually the approach to analysis of the policy is to evaluate the policy and not the process. And did we have the desired impact or a void at the undesired event? And evaluating a process is a much more complex task than actually evaluating the policy itself.

One of the things that I struggled with when I first came to government, because in my previous life in developing policy it was always writing a policy in response to something else, whether it was the Food and Drug Administration or something that a commanding officer or whatever, or a Surgeon General laid down the law, and said, you know, you need to respond to this.

I think the way we approach a lot of policy is that--and I just quote from Clay and Schaffer in 1984, "The whole life of policy is a chaos of purposes and accidents. It is not at all a matter of the rational implementation of the so-called decisions through selected strategies."

So I throw that out there primarily because when you ask somebody, "Well, how was policy generated?", most people like deer caught in the headlights, you know, just what do we do with developing policy? And I think that this whole concept of the chaos is really summed up the statement on chaos. There's also a question whether policy should be linear, and I think that

there's dynamics of thinking of policy formation in a linear process, where you may have the research first and then you move on to the policy. Or you could have it in a cyclic manner. There is a structure and purpose even if it's not see as rational, and I think that that's what I'd like to convey to you today.

We have already seen the IOM report and the 13 individual factors, and I just throw these up again just to show you. I think what's really important about these factors that the IOM responded to is that, you know, you get a multiple number of these factors together and you could have what somebody already referred to the other day as a perfect storm. I think that that's what we're trying to struggle with now is, especially in the cases that have been presented to us, and also looking forward, not looking to what we have today, but also in the future, and do we have a potential perfect storm brewing?

Some of the basics of good policy can be, Anderson said, "A policy can be defined as a

purposeful course of action followed by an actor or a set of actors." And to tease out some of the steps in policy formation was done by Lasswell. But you know, all of this really falls--when I look at the process and a structured process to developing policy, it really falls into the TQM model of plan, do, check and act.

Let me just give you an example here of policy generation. And this is a structured approach, problem definition and agenda setting. And going into that problem definition and agenda setting are really streams of information, streams of influences. The stream of the problem that is out there, the impact on society, the policy itself, the advocacy groups, everything that is pushing and identifying what the problem is.

Secondly is constructing the policy alternatives or policy formation formulation, the choice of solutions or selection of preferred policy options, then policy design and policy implementation, and monitoring and evaluation. I think sometimes though we get to a point where we

really, in doing policy, we may get to the policy design and we stop right there. We don't look at policy implementation and we don't look at monitoring what the policy is, and the evaluation. I think a good example of this is even what we discussed yesterday, was the bacterial detection, reduction of bacterial contamination in platelets. And I think that what has happened over the last year with the push of the task force has been to really identify the implementation and the monitoring and then the evaluation there. So it's an ongoing process.

And if you want to just look at it in the TQM aspect of it, it's the plan and all of these first three steps are really in the planning. The policy design is really the doing, and then the policy implementation and monitoring is checking, and evaluation is acting.

Some of the principles of a good policy process is outcome-oriented, it's forward looking. I think we can look in the rear-view mirror and we can see some of the mistakes that we may have done,

some things, opportunity for change, but we have to be looking forward. It has to be evidence based. It has to be innovative and flexible, open and inclusive.

Let me just address some of the features here. Just as this group meets in a very open environment, clear, we have to have an open process by which we develop policy, so that we get the input that we need and make the right decisions.

We have to have an open and inclusive policy or process so that we have efficient use of limited resources and the financial aspect. One of the things that I've noticed here was, you know, yes, we still have some of the case studies that were presented, and the case studies that were presented, at least two of them, may be a priority of research. And so how do we identify what should be the priorities of research in developing a good policy?

Participation and partnership, I think we've heard that over and over again the last couple of days, of making sure that we have

everyone to the table and that we're making the right decisions.

Outward looking. I think that we probably were called, at least HHS, with the EID Committee, probably took a good message there in the fact that that is internal to the Government, and I think that when we look at policy we have to go out and outward looking also.

Communication. Let me dwell on communication a little bit. Just as I believe Mary Gustafson said earlier, you know, just in real estate there's three words, location, location, location, it's communication, communication, communication. And don't think because you have disseminated something that it has been communicated. You know, you're bound for failure if you think that that is communication.

Evaluate and review, and take lessons learned, and be accountable for the process. If we look at some of the tools and politics that we have, of course you can start off with the streams. I mentioned earlier about the streams being the

politics of a policy, the impact of interest groups, advocacies. So with the tools that we could use for assessment or for the contexts, stakeholder analysis, field analysis, workshops, policy mapping, political context mapping, all of those are different tools that can be used to really tease out what are the issues that need to be addressed in a policy.

Research tools. Case studies, episode studies, surveys, literature searches, focus group discussions, and not to--I see one glaring error here is really the hard science research and the design of that.

Policy influence tools. We go into the linking of the media and the advertising, the monitoring, you know, the influence mapping and power mapping, the lobby and advocacy campaign and coalitions, how to get the word out, the communication tools of the strategy, the strength, weaknesses, opportunities, and threats, and message design and the use of the media to get what we want out.

Some key questions for policymakers and stakeholders. What is the problem to be solved? What is the proposed intervention? What are the known and likely positive and negative effects of the intervention? Do the positive effects outweigh the negatives? How much will the intervention cost? What is required to make the intervention work? How would you ensure equity and sustainability? What options are lost if we adopt the intervention? How often and by what criteria is the intervention reviewed?

Some of the communication strategy. Approach communication as a systematic issue. Communication is not the same as dissemination, as I already mentioned. Communication is a double-loop learning process within the Government with stakeholders and the public. We have to keep the public and the stakeholders and the Government, all three need to be talking. Improve conditions under which research and evidences are communicated. The media can help us with our awareness and our reduced stigma.

Multiple formatting. Words and different media forums matter in different contexts. And assessing policy is the impact on outcome. The assessing and fairness of the policy for different groups and regions of the country. The cost and value added. The scientific evidence to back the policy. The risk. Public health and safety.

Let me just go back to the risk and public health. I think we've heard several times today about the infrastructure of public health, and I think that we really need to be concerned about that in any policies that we put forward, as what is the infrastructure of public health to support that, and how is that in our country?

Legal issues and international agreements, operational capacities and assessments. I go back to legal issues and international agreements, especially looking more as a global approach to the policies that we write and operational capacity assessments.

And then finally the regulatory system impact assessment. What is the impact on the

regulatory system? The conclusion that I would just like to try to summarize here is that the policy analysis checklist and tools are available to help us guide ourselves in forming good blood policies. Process is important. How you did is as important as what you did. And the policy processes are complex, but there are key common components, key principles for success, and some simple common sense approaches can make a big difference. And the response depends on the context of the policy.

I guess the question that we would like to throw to the Committee--and I know that we're short on time--but it may just boil down to what are our next steps, but what are the key components of a strategic blood policy for emerging and known threats to the national blood supply? And how does the Advisory Committee recommend strategic planning for emerging and current threats? And what should be the next steps?

DR. BRECHER: Karen.

MS. LIPTON: It's really hard to get our

arms around this whole issue, but one of the things that keeps coming up I think is a recurring theme, or two themes really. It's communication and it's transparency of decisionmaking. And I want to add a third thing, which is research, but I'll add that at the end.

And it occurs to me that one of the things that we run into is we have organizations that have information and we don't have a well-understood process as to how that gets out. We also have, interestingly enough, you know, with the FDA because of the Public Advisory Committee Act, we have some real problems in getting information out, and how do they invite people in to a meeting in some of those restrictions? As I'm sitting here I sometimes think maybe we're leading with the wrong foot, if you will, or the wrong agency, that--you know, I know the CDC has some issues, but it seems to me that they have a greater flexibility, if you will, to convene groups of interested players to talk about some of these issues. I just wonder if we ought to be rethinking some of this.

I think we do fairly well at what I would call the studied approach to some of these issues that are long term. We have some pretty nice processes in place. We are not very nimble when it comes to emergent problems, and we're all kind of stumbling around how to get information to each other. So that is just something--I don't know that we've deployed our resources or our strengths in the right order or in the right way, just something to think about.

From the scientific and research standpoint, it does occur to me that in some of the issues that were identified there are a lot of research initiatives that suddenly come up and we don't know the answer to, and it does seem to me that having some sort of front for research, whether it's done by FDA or CDC or contracted out to other places, that we ought to have some sort of capacity to do things again in a much more nimble fashion, and draw on the resources. We keep talking about partnerships and using what we have, but I just don't think we're doing it that

effectively.

I don't know the answer. I just think maybe it's better to throw it all up in the air and start over.

DR. BRECHER: Paul?

DR. HAAS: I think Karen's first part, for the research, build on a point I made earlier today, in that this Committee was formed with its eclectic membership to deal with these cross-disciplinary types of things, but from my perspective, I'm sitting here, who's out there to advocate for the public health system which would then help us find the resources to do all of the things Karen and other people have mentioned? And it's an odd situation. How can this body lobby itself or Government to get the resources? And I think that's another one of these balls that are up in the air that we need to try to address.

DR. BRECHER: Chris?

MR. HEALEY: I guess I want to take a little bit of a contrarian view to Karen. Our recent experience with West Nile virus, at least in

the plasma sector, I think we got off to a little bit of a slow start, but ended up having just terrific communication with FDA. And going to the research end of the issue, we went in and met with FDA, and there was some excellent dialog about the nature of the research that needed to be done, and they had input into the process, and industry responded, and there was a real give and take there, and I think some really good outcomes, at least from my perspective, were the results of--I felt like there was some dialog.

I think there's always room for improvement, and I think getting some of the consumers more directly involved in that process may have benefited it, but I think as far as the research goes there was some real good give and take and exchange.

MS. LIPTON: I agree with you on some of the models, but it only works on some of the models. West Nile virus works because it's great. It's viral testing. I think where you get into some weird situations are when it doesn't fit the

models of what we've known, and that's where I--you know, I wonder if we ought not to be thinking about it a little bit differently.

DR. BRECHER: Jay?

DR. EPSTEIN: I just want to try to highlight some of the threads of what I thought were the gap areas or issue areas. I think it emerged a number of times that coordination of the public health response is an issue in its own right, and we looked at inter-agency issues. We also looked at the issue of coordination with state public health authorities. At times we talked about how do we engage the clinician. So it's the coordination of the arms of the public health system is an issue.

I think we also heard that we may not have adequate tools to carry out effective surveillance. Again, there are different dimensions. We are talking about horizon scanning. We're talking about searching for undiscovered agents. We're talking about monitoring currently-known agents and looking for changing patterns. We're also talking

about what's called Phase IV surveillance, which is the impact of products and their safety profiles. So I think surveillance has presented itself as another issue area.

Then I think we have heard that there are issues of prioritization, and these have come forward in two major domains, one of which is the decisional process itself. In other words, what do we decide to work on? What do we think our important issues are? Who gets to decide that? Why is it those people?

And then there's the issue of prioritization of a research agenda. I think that what we heard is that we seem to lack a coherent process to target effort and coordinate effort and fund effort, even if we identify what we think are the issues of the day, that at the very least we don't have a coherent simple process that we understand, not that there's no process.

I think another thread was the quality of risk communication. And it had again a number of dimensions, one of which is transparency, another

of which is timeliness, completeness, accountability, and so forth.

Technology development seemed to be another thread. Many of the problems that we would like to solve or that may yet emerge will require technology solutions, and then the question is, well, what are the incentives for technology development? What does it take to overcome the risk of the manufacturer to invest? What is the role of governmental support? What is the role of regulatory mandates? What is the role of public perceptions and expectations?

And then I think that we also heard a lot about scientific uncertainty, and this gets right to the core of the IOM report in 1995 and why we have a Committee and why we've restructured some of the decisional processes within the Department. It's all about what do you do when you don't have a clear scientific answer? I guess my own reflection is that that is an unending question because you keep being faced with new uncertainties for new problems and each one has its own parameters.

But I think that we have to take on, once again, the problem of decisionmaking in the face of uncertainty, and when is it an appropriate consideration before you act, and you know, when do you have to put it aside and say we need to act in the face of these uncertainties?

So I would summarize all of this by saying that what appears to be lacking is a coherent framework in which to set priorities and target resources for the blood system, and that the problem really lies in trying to establish a framework. And I say that recognizing that it is an extraordinarily complex endeavor, that we're dealing with a large number of organizations, different parties. They have their different mandates. They have their different strengths, weaknesses, limitations and flexibilities, and that is the system that we use.

And I'm optimistic enough to say that it's often worked quite well, but on the other hand, at the times where it has not worked well, the issue really does seem to be the lack of any coherent

framework. In other words, where do you go first trying to make that system produce a right answer or a next answer.

So that's just my take. I don't have answers really, but I think that those were the threads of issues that I heard.

DR. BRECHER: Jay, it seems like in the past, even with a scanty framework in place, anytime there is a perceived major threat, everything goes away, there is no framework any more. It's like--it's chaos, yes. And I don't know how to get around that.

Matt?

DR. KUEHNERT: I think Jay touched on a lot of the points I was going to make, and so I think--but one thing I wanted to really emphasize is that the most important thing in having a coherent framework is making sure that the right partners are there at the table and that all of them are there at the table.

I think one thing that struck me about Hira's presentation was that I thought the most

important slide was probably the last one, which was the acknowledgement slide, which showed all of the partners that basically worked together. And it just, I think, you know, a combination of skill and luck as usual. I think it was lot of skill on the part of the task force, but I also think it was a little bit of luck that all the right partners happened to be there and available and in the right place at the right time. So I think it's important that we really think through who the partners are.

And as Jay mentioned, I think some folks that are missing are the public health partners and the clinical side. I think that we really need to think about where they fit into this whole thing.

Also in looking at the entire spectrum again, I didn't mean to exclude plasma products--I think that is very important--when I talked about a biologic product spectrum, as well as organs and tissues, but certainly plasma products need to be included in considering the spectrum. But I think we can--you know, by having comprehensive inclusion, we're less likely to miss things.

I mean, just to give an example, you know, transmission of that pathogen through organ transplant has been known for years. So, you know, we need to look at that literature and have those individuals with that technical expertise involved as well.

DR. BRECHER: Chris?

MR. HEALEY: Matt, I think your comments are well taken, and I particularly appreciate the ones about the plasma sector, obviously. But as I go through the list that Dr. Epstein articulated, it seems to me there are some pretty clear distinctions between blood and plasma almost down the line, you know, particularly a lot of the technologies are different because of the fractionation process and so forth. Some of the risk assessment, therefore, is different. Certainly the communication is different because there's a concentrated group of consumers who are chronic users of these therapies versus more traditional blood product administration.

So post-market surveillance is another

one, characteristically different because you have products that have a shelf life on the market. So I guess one of the threshold questions I have--and I guess I'd pose it to Dr. Epstein--is: When you outlined these issues, did you envision that this was both blood and plasma? Or did you envision two separate systems? Or perhaps you didn't develop it that far in your mind. I don't know.

DR. EPSTEIN: I don't think there are two separate systems, and I think that when we're looking at product issues, we have to recognize that there are differences among the products.

I think that the set of examples was meant to illustrate the nature of the problems, in other words, where are the gaps. I think we could have come up with examples, you know, for plasma, too. Our hope was that the vCJD would serve as a plasma example, but we could have looked at others.

But, you know, I think from the public health point of view, it's without question that we care about, look about, and consider the issues of plasma products.

MR. HEALEY: To me the question is is it the same group of people at the table doing the work for the plasma as it is the blood. I don't know whether that's one cohesive group or whether you have to have dual tracks.

DR. BIANCO: But CJD is a good example where in the beginning you didn't know if it was blood, plasma, or both, and only later that the process separated. So in the beginning it was everybody.

DR. BRECHER: Also, I think a lot of the recipients of the plasma products also receive blood products. And so I think the two are tied very closely together.

Jerry and Andy.

DR. SANDLER: I think that there are two paradigms for the framework. One paradigm would be a relatively traditional way of more of the same and better organized with what we're doing. And I think the other paradigm is that pathogen inactivation is here, and if it takes up $2 billion a year of the resources, we're in a totally

different ball game.

I think that we have a $2 billion gorilla sitting right in the middle of the room, and if I were to invest in something, I'd like to know whether pathogen inactivation is going to be here or not.

What should be the next steps? To me the next step for this group is to get a better sense of whether pathogen inactivation is a notion or whether it is something in the pipeline that this country is going to buy and clean up a very large piece of everything that we heard. And I would like to propose that the next meeting that we have we take a hard look at that because if it's really to be, it's going to need more than almost an adversarial role from HHS. HHS isn't putting a lot of money into it. We haven't made a statement that says this is the answer to the problem and it's going to end the safety issue. And when you come to FDA, by necessity--by necessity--there's no real rule about how you meet their requirement. Send us what you are doing and we'll evaluate it and we'll

let you know and what have you.

I don't think we have as our government looked at this the way industry is doing it. They're doing it sort of by themselves. And they're really pushing it. To me the next step is find out where that fits into the puzzle because it's either one framework or the other.

DR. BRECHER: I would take exception to your comment that it's here, because I don't--it's not here yet. And if you were to invest in it, then you'd have to declare your conflicts. But that aside--

DR. SANDLER: That was figured into it.

DR. BRECHER: I know. But that aside, one possible topic for our next meeting would be to explore many of these emerging technologies rather than threats that would impact on the future of both plasma products and blood products. That's one possible agenda.

Mark?

MR. SKINNER: I'd just like to refine just a little bit what you said, because I agree with

Dr. Sandler. I mean, we're going to be talking--there's always going to be new things coming on the horizon, and the real solution is the robustness of either the inactivation process or the viral clearance process, part of what I said before. And I don't want to just identify what we need. I would also be curious if we know what the barriers are to achieving those beyond dollars. If it's regulatory or if, you know, there's competitive barriers or whatever the issues are that prevent those things from occurring, because I've heard over the course of time there's different things that companies want to do, but it either takes too long or regulatorily it's too difficult or there's different sets of standards that provide competition. So if we can drill down beyond just what do we want but what prevents that from actually being here today.

DR. BRECHER: Andy?

DR. HEATON: I'd like to add a couple of thoughts to the debate.

First of all, one of the fastest growing

sectors in the transfusion and transplantation market is that of tissue. It's a very rapidly growing area, and it's an area that is not yet subject--or does not have the same level of maturity with respect to risk assessment. So one area that I believe that we need to pay serious attention to--at the moment we keep talking about whether plasma should be included with whole blood regulations. I think we need to consider very carefully whether tissues, semen donors, breast milk donors--there's a whole range of different biological products that are moving from one human to another, and they convey exactly the same infectious disease risk as those we're discussing.

So I do believe that we should seriously consider the scope of what we're talking about and whether this committee should pick up tissues.

DR. BRECHER: Don't forget cellular therapy.

DR. HEATON: Yes, and cellular therapy.

Then in the second area, Jay was talking about to the issue of targeting and prioritization,

but targeting resources. Now, as you look at the West Nile virus example, which is a very good example of good targeting and good focus, there was a very clear sense of direction and market, and, therefore, the resources were available. Many of the new threats, like HHV-8, for example, simply don't look like they have the economic opportunity that people will speculatively invest large sums of money in assessing those risks. So a key player for us and a player who's always at the edge of our discussions and never gets into the center of the ring is NHLBI and government funding. And we very much need resources to target, and we have a vast government agency with a huge and very privileged funding line, and I believe that there is much that they could do to support many of these initiatives and to assess--and to provide the scientific basis on which to reduce the uncertainty that would allow us to make a better decision. And I see them as a key constituent in any decisionmaking or prioritization process.

DR. BRECHER: Celso?

DR. BIANCO: I think that we have to go to something a little bit more concrete before we leave the room today. And I think maybe we are getting there or not. I think that we didn't talk about it, but the biggest difference between the beginning of Dr. Katz's presentation, 1983, and today is our sensitivity; that is, we, everybody in the field, behaved differently to a perceived threat. At that time it was denial, and very little, and today it's almost to the other extreme, it's overreaction and we are trying to manage our priorities and the resources that we have.

So I think that the things that were raised here by Jay, by Karen, by almost everybody, there is a communication network, transparency of what we do, but a communication network is the first thing that we have to work on. I think Jerry Sandler is correct, but we'll have many months, many years before we get there, Jerry. And while we don't get there, we need that communication network.

So I think that we have even to move and

ask who would be the mother of that communication network, how would it be managed, and there are many examples around. Many of us subscribe to a simple thing like ProMed and open our e-mail every morning and have two, three e-mails with things that are happening around the world if they have some implication or not. We need the ProMed blood or something of this kind, and we need to know those partners that we are communicating with and how we do it.

So I suggest that we start walking more concretely, more pragmatically to the things that we can do, and essentially to respond to the questions, to the gaps that Jay raised very eloquently here.

DR. BRECHER: Karen?

MS. LIPTON: Celso, I really agree with you, and I maybe didn't express it the right way. I mean, that's what I think the problem is. I think that if you look, for example, FDA has some materials that would be helpful to us to have and to start working on. It's not that they don't want

to give it to us. It's that they have some barriers and processes and things they have to go through. So the question is: How do we set this up to all be involved more, the people who are expert and who are doing it, you know, in the discussion from the beginning? And as you said, it really is just communication so that we all have the same information. It should not be an exclusive club. I think we've learned that everybody has something to bring to this table, and the more we share these things, I think the better the decision is.

I've just been concerned because I know this Advisory Committee Act just becomes problematic for us to work around, and so are there ways we can work around it to get people to the table faster?

DR. BRECHER: Jay?

DR. EPSTEIN: Well, I have to push back a little bit, Karen, because I don't think the central problem really is the Advisory Committee Act. That issue really focuses on the timeliness

with which we get information out before public meetings. But to focus on that misses the larger picture that we have an enormous number of public meetings. You know, we have Blood Products Advisory Committee, a TSE Advisory Committee. We have scientific workshops. We participate as liaisons in private sector meetings. You know, we present and share scientific data at scientific symposia. We post information on the website. You know, it goes on and on and on and on and on. And that's not even looking at the formal processes of guidance publication through notice and comment and rulemaking.

So it's not a deficiency of communication. What is troubling you is the paradigm through which certain meetings are convened, and we understand that concern, and we are working to try to streamline the processes such that information can come out earlier and so that the public, including, you know, the affected parties, regulated parties, can become aware of the issues that concern FDA well before we're at an Advisory Committee.

In other words, we hear your complaint, but I think that it's not the central focus here, or shouldn't be, on what's the matter. Because if the issue is how we debate subject matter, there's plenty of debate of subject matter. Just think how many meetings we have in any given year on any significant issue.

So I don't quite share the view that you're putting forward, Karen, and I don't think it's quite the right--

MS. LIPTON: I'm not speaking, Jay, to the long--I'm not talking about the Advisory Committee meetings themselves. I'm talking about the ability to react quickly, and as an example, not even talking about a meeting, I'm talking about getting the information out that we were talking about, about all the different viruses and pathogens we're looking at and what's known about them. It's really what I call an information exchange. It really isn't the Advisory Committee. I think that works fine when the process can be deliberative. It's this other issue that I think Celso is talking

about. We need a communication network to get information out quickly to everybody. And some of the information you have, some of the information you don't have. But it's really how do we all share this?

My only comment about the Advisory Committee Act is it's very difficult for you to call a meeting immediately and say we need to talk to all the players. That's the only issue. I think it works fine--we're tinkering with the Advisory Committee Act in terms of when you have something on the agenda and how you get those issues before the committee. And I think that's fine. I just think that there needs to be another way of communicating more quickly when we are in a more crisis-driven mode.

DR. BRECHER: All right. We are well below our quorum. I don't see that we're heading toward any resolution here. We have put a lot of topics on the table that I think will be meat for the next meeting.

DR. KUEHNERT: Could I just say that I

support the comments that have been made on the communication network. I think that's something that needs to be followed up on specifically.

DR. BIANCO: Can CDC take care of it?

DR. BRECHER: Is it infectious?

[Laughter.]

DR. KUEHNERT: I think we could discuss it.

DR. BRECHER: With that, I think we're going to adjourn this meeting, and thank you for participating.

DR. HOLMBERG: Before we adjourn, there is--this is a special day. I understand it's Paul Haas' birthday.

DR. BRECHER: Does that mean we all have to sing?

[Laughter.]

[Whereupon, at 3:37 p.m., the meeting was adjourned.]