EMERGING INFECTIOUS DISEASES: EVALUATION TO IMPLEMENTATION FOR TRANSFUSION AND TRANSPLANTATION SAFETY (DAY 1)

EVALUATING EMERGING INFECTIOUS DISEASES (EIDs) FOR TRANSFUSION SAFETY

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620 Perry Parkway
Gaithersburg, Maryland 20877

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LIST OF PARTICIPANTS:

C.D. ATREYA
Associate Director for Research

HIRA NAKHASI
Director, DETTD, CBER

CAROLYN WILSON
Associate Director for Research
CBER

JAY EPSTEIN
Director
Office of Blood Research and Review
CBER

JAMES HUGHES
Professor of Medicine and Public Health
Emory University

MATTHEW KUEHNERT
Director
Office of Blood, Organ, and other Tissue Safety
CDC

MARTA GWINN
Medical Epidemiologist
Office of Public Health Genomics
CDC

STEVEN KLEINMAN
Senior Medical Advisor, AABB
Clinical Professor of Pathology
University of British Columbia

Roger Y. Dodd
Vice President, Research and Development
Holland Laboratory
American Red Cross
SUSAN L. STRAMER
Executive Scientific Officer
Biomedical Services
American Red Cross

PETER R. GANZ
Director
Center for Biologics Evaluation Health Canada

MARK WALDERHAUG
Associate Office Director for Risk Assessment
Office of Biostatistics and Epidemiology
CBER

JERRY A. HOLMBERG
Senior Advisor for Blood Policy
HHS Office of the Secretary

HARVEY ALTER
Chief of Clinical Studies
Associate Director for Research
Department of Transfusion Medicine
NIH

RAYMOND P. GOODRICH
Chief Science Officer
CaridianBCT Biotechnologies

CLARK TIBBETTS
Executive Vice President
TessArae, LLC

DAVID ASHER
Chief, Laboratory of Bacterial, Parasitic, and Unconventional Agents
OBRR, CBER

PAUL A. MIED
Deputy Director
Division of Emerging and Transfusion Transmitted Diseases
OBRR, CBER
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ADJOURNMENT

* * * * *
MR. ATREYA: My name is C.D. Atreya. I'm the Associate Director for Research, Office of Blood Research and Review. Myself and my colleague, Dr. Hira Nakhasi, Director for the Division of Emerging and Transfusion Transmitted Diseases in our office will be your point of contact for today. And then for tomorrow, Dr. Melissa Greenwald, Chief, Human Tissue and Reproduction Branch, Office of Cellular Tissue and Gene Therapies will be your contact person.

I have a few comments and announcements to make. First of all, I would like to acknowledge the hard word of a few dedicated staff from our office and from OCGT, who have been taking care of numerous aspects of this workshop and they are my colleague Jennifer Scharpf. She is the associate director for Policy in Office of Blood. And her staff, Rhonda Dawson, then Heather Gucha (phonetic), Jim Durham (phonetic), Kim Hubbard (phonetic), Paula Gable (phonetic), Rosemarie Wiseman, Risha Schecter (phonetic),
and Felicia Jackson (phonetic). They have all done excellent work of putting these folders together, taking care of every, you know, fine details of this workshop.

Second, I would like to announce that we would like to publish this workshop proceedings in a peer review journal and for that I request all the speakers to provide me with a brief write-up of their talks, what they are presenting today. Say by a month from now, something like June 11th, I will send you a soft e-mail first time and then thereafter every other day as a reminder. Just kidding, you know, just kidding.

Third, for your lunch options, there are a few things available. One, in this hotel itself, there is a restaurant that you can go and have your lunch. And if you are driving or if you prefer to walk in this little cold weather today, a couple of blocks from south of this side, there are some restaurants which you can have your lunch. But I request you all to come back on time to attend your post-lunch sessions. Don't enjoy too much there.

The third one is -- I think that all for the announcements. So without further due, I invite my colleague Dr. Carolyn Wilson, who is the Center Associate
Director for Research to provide her welcome remarks to open the workshop for business today. Thank you. Carolyn.

WELCOME ADDRESS

MS. WILSON: Thank you C.D. And good morning and welcome to this workshop. For those of you who were expecting Dr. Mithun (phonetic), I wanted to just share that she sends her regrets. She was called away quite at the last minute; I think it was about Friday that she found out she would have to be out of town this week.

So before we begin, on behalf of the Center and Dr. Mithun, I want to acknowledge the important contributions that have made this workshop possible. First and foremost, of course, we thank all the speakers, the discussants and the participants for accepting the invitation to share their time and their expertise. We are grateful for the diligent work of the workshop planning committee, a genuine collaboration between the FDA and our HHS partners. Represented agencies included the Department of Health and Human Services, Office of the Secretary, Office of Science and Public Health, Health Resources
Services Administration, NIH and the CDC.

The committee representatives who made this possible are co-chairs, Dr. C.D. Atreya, Hira Nakhasi, Melissa Greenwald; CBER members Jennifer Scharpf, Mark Walderhaug, Richard Davey, Basil Golding; NIH members Harvey Alter and Simone Glynn; and CDC members Matthew Kuehnert and William Bower; Jerry Holmberg from OSPH; Elizabeth Ortiz-Rios from HRSA.

We are holding this meeting today and tomorrow to provide an opportunity to review the strategies used for identification, prioritization and response to emerging infectious disease that are relevant to blood cells, tissues and organs. As I am sure you know, CBER is responsible for maintaining the safety of the blood supply as well as tissues used for transplantation, both essential public health interventions. However, there is a constant challenge to this responsibility due to new threats from potential agents of bioterrorism or naturally emerging infectious disease.

As we all know, we live in a rapidly changing global environment where exposures to infectious agents are evolving due to a number of influences such as spread of
disease factors, travel, immigration, emergence of previously rare unknown pathogens, and we'll be hearing a lot of examples about this over the next two days.

However, with each emerging threat to the blood and tissue supply, there is a careful balance that must be met looking at the cost associated with the impact on blood supply availability, risks associated with the transfusion or transplantation transmitted diseases, and the time and effort involved in developing and implementing new test methods.

So the challenge to the community and to you as participants in this two-day workshop is to develop those processes for early threat detection, prioritization and risk reduction of emerging infectious disease agents that are relevant to blood cells, tissues, and organs.

Finally and importantly, an additional goal of this workshop is to facilitate dissemination of scientific knowledge among government, academic community, and regulated industry with a goal to device strategies to ensue the safety. FDA values and is seeking your input to address these critical public health issues and we are looking forward to fruitful discussions over the next two
days. Good luck and again thank you for attending and contributing to this two-day event.

INTRODUCTORY REMARKS

DR. EPSTEIN: Good morning everyone. I'm Jay Epstein, the director of the Office of Blood Research and Review. It's a pleasure to be here this morning with you and I thank you for this great turnout for what we hope would be an informative and thought provoking workshop. So it's my pleasure to provide a little bit of stage setting about the whole question of emerging infectious diseases and how we look at trying to maintain a safety of blood for transfusion and tissues for transplantation.

I should start though by explaining the larger context of the Center for Biologics Evaluation and Research. Our overarching vision is innovative technology advancing public health, and within that framework we seek to protect and improve public and individual health in the United States and where feasible, globally. We facilitate development approval and access to safe and effective products and promising new technologies, so it's a forward
looking concept of facilitation and we seek to strengthen our own selves CBER as a preeminent regulatory organization for biologics. Now within this vision we have several cardinal strategies.

First, is to enhance the nation's preparedness. That is to assure the nation is prepared for emerging infectious disease threats and terrorism. I think it's self evident that the subject matter of this workshop fits within our broad mandate of preparedness.

Secondly, to keep products and patients safe. And to do this we seek to harness the power of bioinformatics at the population, patient, and molecular levels to monitor and enhance safety, improve the risk/benefit and ensure good public communication. We see this as part of our role in what we call 21st century medicine.

And then third strategy is innovative products to patients - a critical path. This is the research piece. This goal involves advancing science and technology to permit better prediction of product safety and efficacy, thereby facilitating the availability of novel products to address unmet needs.
And I won't spend time elaborating on critical path, but it's a broad program which is cooperative with non-governmental funding sources and where we try to leverage effort with the unique role of the FDA as regulator and the essential need for a laboratory underpinning of what we do.

Now, turning then to the subject matter of today's workshop, I've just listed here a short list, if you will, of emerging infectious agents that have been of recent or current concern to blood safety. And on the left side you see that we've had recent -- relatively recent interventions for West Nile Virus since the unprecedented massive U.S. outbreak in 2002, very rapid response with innovation and nucleic acid tests which were in place already in 2003 and then the evolution from minipool testing to triggering of individual unit testing because of low tidal viremia.

More recently, we have issued guidance on the use of a test to screen for antibodies to Trypanosoma cruzi. This is a long-standing problem and it gets to the heart of what do we mean by an emerging disease. Sometimes it's recognition and response that emerges. Be that as it may,
ultimately we had the development of very sensitive and specific donor screening tests, and lo and behold, studies have suggested a whole new debate about the question of whether there is any significant incidence in this country or whether you can test the donor once because of acquisition generally as a child in an endemic area of Central or South America.

Now on the right hand side, I have a shortlist of things that we're worrying about right now, where we're talking about the underlying science and whether there is a threat and how it ought to be contained and what strategies might be effective. So we're concerned about Dengue viruses.

Many of you know that we've had outbreaks in Florida, the Texas, Mexican Water, Hawaii, Puerto Rico that the Red Cross voluntarily does not import blood to the continental U.S. when there are outbreaks in Puerto Rico. Questions about the utility of NAT or an Antigen Test for Screening; again very active but no solution yet.

Babesia is going to be discussed in detail, raises the whole challenge of a geographically abounded risk or relative risk. XMRV and an even earlier stage, you
know, is it transfusion transmitted, is there a disease association? Even are there serologic findings reproducible by different groups?

Chikungunya Virus, outbreaks in various parts of the world. There have been imported cases in the United States. The whole question of what's the potential for spread in the United States and how aggressively do we need to prepare?

Leishmania, we have voluntary donor deferral policies because of cases that have been acquired in Iraq and Afghanistan. The whole debate about visceralizing versus cutaneous disease, a few dogmas are perhaps shaken when cutaneous strains proved to be visceralizing a minimum amount of known transfusion transmission and yet some proven infectivity in blood.

Q Fever, we have a unique outbreak going on in the Netherlands and the whole question of how significant the threat is that in the United States and against what background. After all, we do have a Q Fever here in -- you know cattle, sheep, and goats, and we do have some baseline, and you know, we would be acting disproportionately if we had a policy addressing the
Netherlands.

So these are all very, very active and I mention these because each one is its own case and presents us with some different questions. But we do have some general frameworks and that's what I'm illustrating now in this slide.

We have a general safety strategy which we call — for blood at least, the five layers of blood safety. First is donor screening and deferral based on risk factors. These risk factors are determined epidemiologically. They include geographical exposures such as for malaria or exposure to Mad Cow Disease in certain parts of Europe predominantly.

Behavioral, for example, intravenous drug use and medical risk factors, certain procedures. We then of course have laboratory testing which you all know. Either of these can lead to either a temporary or permanent deferral based on different markers, different risks. We then use deferral registries. These are lists of deferred donors and the concept is to prevent either the collection upfront or if there is a collection, the use of blood collected from a deferred donor. So it's again an added
safeguard.

Principally, the idea is to try to keep contaminated units out of the inventory before there is ever collection, but we do know that the registries could not always be checked in real-time on mobiles, so it's a mixture of upfront and backend controls.

On the subject of controls, quarantine controls are critical safeguard because we know that we will be collecting blood that later tests positive and we want to make sure that units do not get released inappropriately. This of course is facilitated by computerization.

And lastly and -- but of no lesser importance, good manufacturing practices at all levels which include of course aseptic procedures, you know, ensuring freedom from environmental contamination, proper conditions of refrigeration and so forth, but the investigation and correction of deviations.

We have reporting of deviations which we used to call errors and accidents which leads to insights about how the system is working or not working. And then we respond to those by engineering additional safeguards. So this is an important, you know, learning element of continuous
And then lastly, I would mention that although we do not have it in place at this time for products for transfusion, pathogen reduction technology is, if you will, a Holy Grail. There are technologies that are actively being developed. Some are already approved in other countries.

In no country is there pathogen reduction technology for all of the transfusable components, and hence the use of other tools, deferrals, and testing is in place still worldwide. But ultimately, the goal is to have pathogen reduction for all of the transfusable components. We already have it in place for all but a handful of plasma derivatives.

So turning then to the workshop itself, I just want to outline some of the basic issues that we confront as FDA and the public health service when dealing with an emerging infectious agent or disease. First we ask whether the agent is blood borne and is it viable in blood and in tissue, particularly, will it survive product collection, processing, and storage? Some agents don't and so you know we were always relieved when we learn that and we always
ask that question, but of course many do.

Then there is the question of prevalence in the donors. You know we don't want to, you know, chase phantoms. So it's important that scientific studies should be done to establish the prevalence because that will then govern the risk. Then is the question of transmissibility. Again, by transfusion or transplantation some agents are readily transmitted, some are relatively hard to transmit and then there is the -- you have to then combine in order to estimate a risk. You look at the prevalence, you look at the stability and storage, you look at the transmissibility rate, and then you want to know whether there is any asymptomatic period in the donor.

Why that's critical is that we select for persons who are in good health. But there are many agents either in the prodromal phase of an illness, excuse me, or in a chronic carrier state that are asymptomatic when they are infectious. And this of course also governs risk on a statistical basis. What is the duration of infectivity pre or post infection or illness or with chronicity?

And then lastly is the question of the disease attack rate and the clinical impact on recipients. What is
the likelihood of getting the infection, what is the likelihood of being ill and what is the medical significance of the illness? And then all of this factors into what is the appropriately measured response.

So then we come to the question of safety interventions. If we've then decided that an agent or disease, we don't always know the agent of course, an agent or disease warrants an intervention, we then have to figure out what is feasible to do. Can we screen donors for risk factors?

Generally speaking, we know more about the epidemiology and can define risk factors than we do about tests in the early stage. There is usually a delay. And so we tend in the early stages of addressing an emerging condition to lean on risk factor based donor exclusion. That always suffers the problem of low sensitivity and low specificity.

We know that, but on the other hand, the screening procedures based on risk factors tend to be somewhere in the ballpark of 80, and even in some cases 95 percent sensitive. And so we use them in order to reduce the number of contaminated collections. Whether they
should stay in place after we have the availability of better interventions, such as testing or inactivation or perhaps sometimes leukocyte reduction is then an independent scientific question which is -- typically bedevils us. Often times, the behavioral or geographical exclusions persist because we see them adding value but we're not sure how much.

Of course, testing is valuable whenever we can do it. And then -- but the question about tests is whether the available tests are sufficiently sensitive to provide a meaningful safety benefit. And let me just say that FDA does not hold out for perfection. If we have a serious condition we will intervene. So for example, the first generation screening tests for Hepatitis C were about 70 percent sensitive. We learned this mostly in retrospect, of course, but it was not a reason not to institute the available test.

Then the question also was whether the available tests are sufficiently specific to avoid compromising product availability. It's very problematic to have high false positive rates. Generally speaking, because the prevalence in donors, because donors are already
prescreened to be healthy individuals with low risk exposures, the positive predicted value will be low. That is to say that the ratio of false positives to true positives will be high, often in the range of 10 to 1, that would not be rare.

And we have to accept that, in return for the benefit of sensitive screening, but it's with the understanding that we always endeavor to find strategies to characterize or confirm the true positive distinguished from the false positive and reenter the healthy donor. It's not always achievable but it is always the goal.

And then lastly, is the whole risk benefit question, can the system bear the burdens of screening and testing? This is the practicality issue. Now, in FDA terms, it's not framed solely in cost. And we know that there are debates about cost, and cost effectiveness, infrastructure feasibility, and so forth. We frame that as a risk benefit.

And then lastly is the question of suitable alternatives. In other words, must we always be on the paradigm of donor deferral and testing. And of course, as I said, we have the Holy Grail of substituting pathogen
reduction for some but perhaps not all of the deferral and testing strategies based on the effectiveness for the agents.

So the motivation for this workshop is to explore the strategies for emerging infectious disease, threat detection, intervention and then the prioritization of effort. And I believe that this has two essential subparts. The first is the characterization of the risk to blood, cell, tissue and organ safety from emerging infectious diseases and the recognition that that is often difficult.

And then secondly, we have this objective to discuss prioritization and I think the key point here is that there is no ideal prioritization process, especially when we're looking at multiple EID agents concurrently that may threaten product safety. So how do we get our arms around that? Is it at all times the old court press or can we say well we're going to deal with this agent today and that agent tomorrow?

Now, just briefly on the structure of the workshop. I mean you all have the program in your folders. Day 1 is oriented to looking at blood transfusion
safety; again, identification, surveillance and prioritization of EID agents of concern, discussions of methodology and some perspectives shared both in the U.S. and in Canada.

Another major theme would be looking at the tools that we use to address the emerging infectious diseases. What is the prospect for pathogen reduction technology? How are detection tests improving, especially microarrays and these deep-sequencing restructuring types of technology?

And then the specific problem of prion detection, which is no less conventional than the agents itself. And then a round table discussion and future plans hopefully to synthesize what's been heard from all the expert speakers and to try to chart something of a path forward.

Day 2 has a similar structure but is devoted specifically to cell, tissue and organ transplantation safety. Again, approaches to threat assessment in the U.S. and Canada, epidemiology and modeling to evaluate risk, current and future research, a round table discussion, and some closing remarks.

You know, as I'm sure you're also aware, there is
a third day which is a related workshop to talk about risk modeling. And that would be hosted by our Office of Biostatistics and Epidemiology at FDA and we'll look at some of the examples of how we have used formal risk assessment models to look at emerging infectious disease and assist in policymaking.

So I'm going to close my talk again to acknowledge our partners. Dr. Wilson already mentioned them, but I shall again; HHS Office of Science and Public Health, Centers for Disease Control and Prevention, National Institutes of Health and the Health Resources and Services Administration. And we're very grateful for all that support. So now it's my pleasure as well to introduce our keynote speaker James Hughes.

Dr. Hughes is the -- is currently professor of Medicine and Public Health at Emory University. He received a bachelor's degree and a medical degree from Stanford University and then trained in internal medicine at University of Washington. He trained in infectious diseases at University of Virginia, and then trained -- I think a little ordeal by fire, at the Centers for Disease Control.
At CDC, he started an illustrious career as an EID officer and later advanced to becoming the director of the National Center of Infectious Diseases from 1992 to 2005 before leaving to join Emory University. He is currently a senior scientific advisor for infectious diseases to the international association of National Public Health Institutes. He is the president-elect of the Infectious Diseases Society of America -- I'm a proud member. He serves on the Council of the American Society for Tropical Medicine and Hygiene and the American Association for the Advancement of Science. He is a member of the International Board of the American Society for Microbiology, and he has a very wide-ranging research interest including emerging infectious diseases, antimicrobial resistance, vector borne and zoonotic diseases, food borne and water related diseases, health care associated infections, disease surveillance and public health laboratory capacity building.

We are indeed honored and privileged to have Dr. Hughes here today as our keynote speaker. I can't imagine a better student -- individual of such a scope and breadth. So thank you and pleasure to have you here, Jim.
EMERGING INFECTIONS: LESSONS LEARNED AND IMPLICATIONS FOR THE TRANSFUSION AND TRANSPLANTATION COMMUNITIES

DR. HUGHES: Thank you. Thank you very much Jay for that very kind introduction. Can everybody hear me okay, way in the back there, okay, looks like it. Well, I would like to first thank the organizers very much for the opportunity to participate in this very important and timely conference. And I think you've already heard very eloquently why we're all here and why we're all rightly concerned about what the present and the future have to hold in terms of emerging infectious disease challenges. I would also like to thank one of my former colleagues from the CDC, Dr. Matt Kuehnert, for loaning me a few of the slides that I'll be using here today.

By way of disclosure I have no conflicts with this presentation. What I will do is give you an overview of emerging infectious diseases and a lot of the issues that I'm going to raise have already been alluded to in the opening remarks, but I'll focus on factors contributing to
the emergence and spread of infectious diseases. Some recent emerging infectious disease challenges including a couple of the ones that were mentioned.

Some of the lessons that I think we've learned over the years and some comments about a way forward. But first of all, to remind you of trends in the United States and infectious disease mortality during the 20th century. And you can see, largely as a result of multiple public health interventions and the introductions of vaccines and antimicrobial agents the tremendous reduction in infectious disease mortality that incurred throughout the century, you see obviously the large pandemic influenza peak in the 1918-'19 dramatically depicted there.

But also on the insert there, in the upper right, you see some of the trends in infectious disease mortality since 1980 with the increases noted from about 1981-'82 up through 1996 largely as a result of HIV infection and AIDS, but also pneumonia and blood stream infection.

The fact that mortality diminished as much as it did, led a lot of people in the middle part of the decade to think that infectious diseases had been largely dealt with, and this one of the quotes that many of you have
probably heard before from Sir Macfarlane Burnet, a Nobel laureate, who wrote in 1962, "One can think of the middle of the 20th century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious disease as a significant factor in social life." Now that's complacency, and all of you who were listening to the opening remarks are not guilty of being complacent I'm sure or you wouldn't be here.

In 1992, the Institute of Medicine issued a very important report on this concept of emerging infections. The committee made a number of important contributions in this report. The committee was chaired by another Nobel laureate Dr. Joshua Lederberg and Dr. Robert Shope, neither of whom were guilty of complacency. They provided a definition that I think we ought to keep in mind over the next 2 days. "New, reemerging, or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future."

This slide is an attempt to illustrate just some of the dramatic examples of disease emergence or reemergence that have occurred over the last 15 or 20
years. You should find one or more of your favorite diseases somewhere on there. If you look at all those and you think about them, one characteristic that many of them share in common is transmission either by the vector borne route or directly from animals to people.

So these are vector borne and zoonotic diseases, many of them. We'll come back to that a little later in the talk. It's an important point for us all to keep in mind.

The committee also identified six factors that they felt were very important in contributing to disease emergence and reemergence. You'll remember this is 1992. Changes in human demographics and behavior, population growth among them, advances in technology and industry. Think about the food industry in the United States and the way that has changed over the years as an example.

Economic development and changes in land use patterns. International travel and commerce; microbial adaptation and change; the response of microbes to evolutionary pressures which is one of the features that make infectious diseases unique and ever challenging. And then finally and very importantly, breakdown of public
health measures as a result of the complacency.

Now in 2003, the IOM revisited this arena and they did it again with Dr. Lederberg cochairing the committee. And his cochair this time was Dr. Margaret Hamburg, your commissioner. So you have in a lead role in FDA someone who is extremely familiar with all of these emerging infectious disease concepts and experiences.

This committee identified seven additional factors. They validated the original six, added seven more, human susceptibility to infection, climate and weather, changes in ecosystems, poverty and social inequality, war and famine, lack of political will, and last but certainly not least in today's world, the intent to harm, intentional bioterrorism.

They provided this graphic to illustrate this complex interaction with humans and microbes here in the center and their interactions influenced by these various factors which they can group -- which they grouped into genetic and biological factors, physical environmental factors, ecological factors, and then social and economic factors.

(Discussion off the record)
Okay, I'm going to just visually illustrate a few of these factors. Human demographics and behavior. The slide on the left there is a photograph from Dhaka, Bangladesh, one of the mega cities in the world. In the upper right you can see a wet animal market in Southeast Asia, and in the lower right, a water collection site that's used for many other things in Sub-Saharan Africa.

This mega city idea is one to keep in mind. Thinking of that picture of Bangladesh, if you're a microbe and you are in that sea of humanity, regardless of what your preferred mode of transmission is, I think you would agree your chances of moving around are pretty good.

Trends in mega cities are not encouraging. In 1950, there were two cities in the world with populations of 10 (million) or more people, both of those were in the developed world. In 2007, there were 19, three quarters of them in the developing world and you can see the projections there through 2025.

International travel and commerce is increasing to all parts of the world. As you know, this became of particular interest to everyone during the SARS experience and more recently during the influenza pandemic. This
slide is a depiction of the global aviation network that shows air connections between the 500 largest international airports in over 100 countries around the world.

This is a slide that shows cargo vessels at sea at a given moment and this -- you know, we all think about the airplanes, we don't think about the sea traffic that's moving around. And obviously, these vessels are moving a wide variety of commodities, animals, food products, humans, and microbes. And lack of political will, something to keep in mind constantly, and this results from the complacency that we've talked about.

One of the more dramatic examples is in the polio world and all of you are well aware of the intense global effort targeting eradication of polio globally with four remaining endemic countries, one of which is Nigeria, which back in 2003-2004 in the northern part of the country, a decision was made by political leaders to discontinue polio immunization.

It's a long and complicated story, but as a result of that wild polio virus was reintroduced into 20 countries in Sub-Saharan Africa, the Middle East, South Asia, and as far away as Indonesia as a result of that
So SARS, we all remember SARS. We shouldn't forget SARS. As you may recall, the outbreak began in November of 2002 in two different areas in Guangdong Province and in South China. But it really didn't surface internationally until February 11-12, 2003 when China reported 305 cases of acute respiratory syndrome occurring in Guangdong Province.

It's interesting they did this one day after there was a message on ProMED-mail that many of you may be familiar with, reporting on the occurrence of severe unexplained cases of pneumonia in South China. So that may have had some influence on Chinese authorities and reporting.

And then we have the famous Hotel M, the Hotel Metropole in Hong Kong that this incident, I think, this event represents the most dramatic event that I observed during all my years (off mike) Dr. Leaving (phonetic) alluded to with a transmission of that in this hotel over a 24-hour period from an ill physician who came from South China, from Guangdong Province for a family wedding, checked into the hotel ill, went up to his room in the
ninth floor, didn't leave for 24 hours and when he left he went directly to a local hospital.

But somehow, while he was there he managed to transmit his infection to more than 10 other guests in the hotel, most of whom were staying on that ninth floor and these people went on to become ill, to be admitted to hospitals locally in Hong Kong, but also to, during their incubation period, traveled to a number of other geographic locations Vietnam, Singapore, the U.S., Ireland, and Canada where they became ill and then transmitted their infection to family members and health care workers primarily with the disastrous results that we were familiar with.

So any time someone says we're making these things up or we're exaggerating the potential rapidity of global spread, remember the hotel in -- (tape interruption) -- in South East Asia and Southern China to concerns about avian influenza, H5N1 influenza, and lots of activities to try to control this problem, and then obviously, the (off mike) with the influenza pandemic, a different virus originating in a very different part of the world.

Recently -- (tape interruption) -- but it's very important that we fight the complacency and continue to
work on being prepared for these challenges and do the best we can to detect these problems early and anticipate their consequences which is very much on the mind of everybody here in this room today.

So a lot of this comes down to public health surveillance, a definition provided by another former CDC colleague Dr. Steve Thacker is as follows: Public health surveillance is the ongoing systematic collection, analysis, and interpretation of outcome-specific data closely integrated with the timely dissemination of these data to those responsible for taking public health action to prevent and control disease or injury. So as you all know, I believe, its collection, analysis, interpretation, and feedback for action that's crucial.

We have lots of systems in place to help us do this but whether it comes right down to it, it's the alert frontline health care workers that are critically important. And this slide contains a photograph of one of those, Dr. Carlo Urbani, who was the WHO physician working in Hanoi when one of those ill individuals who, with SARS, who had acquired the infection in the Hotel Metropole traveled to Hanoi, got ill, and got admitted to the
hospital where Dr. Urbani encountered him.

He rapidly recognized that something very unusual was taking place. He insisted on the implementation of infection control strategies in the health care setting which undoubtedly minimized a lot of the transmission otherwise would have occurred in Vietnam. Unfortunately, as a result of his involvement in this, he did acquire the infection and did die, and in fact a specimen of his was the source of the virus isolated -- the initial virus isolated at CDC.

But these alert health care workers or clinicians, laboratorians, veterinarians -- we're going to come back to that -- research scientists, and public health officials. Just a few comments about West Nile, the opening speakers have already reminded us of this event which is here to stay.

But as you recall this was discovered in 1999 in New York City, in Queens in fact, by an alert veterinarian and an alert clinician. The strain was genetically identical to a virus circulating in Israel; its means of importation was and still is unknown. And there has been little subsequent genetic evolution from that 1999 strain.
Those of you involved back in 1999 will remember that the spectra of bioterrorism was raised when this event was first detected.

And one of the reasons this became such a problem for the blood supply and for the transplantation community is this issue of asymptomatic infection which is very common with West Nile; in fact, the vast majority of the infected people are asymptomatic. To compound the problem, the peak viremia in infected individuals who go on to become ill occurs before they become ill.

So just to remind you the geographic spread of this. This shows the experience of 1999 with the infected counties up in the New York City, Connecticut, New Jersey area, 2000 spread primarily in the Northeast; 2001 the spread down into the South East and sub-movement out into the Midwest, and then a very big year in 2002 with spread through the Midwest and into the Rockies.

This 2002 was the largest number of West Nile virus, severe neuroinvasive disease ever documented, and as a result there were new clinical syndromes recognized and there were five novel modes of transmission. And as you know, two of those involved transfused blood and
transplanted organs.

Now, this is an example of the public health agencies and others and spreading -- springing into action very rapidly and implementing very effective public health interventions to protect the blood supply. So congratulations to all involved in that. But the experience certainly did raise questions about transplants as well and here is where the pathologists come into play. I always like to put in a plug for developing good relations with your pathologist because they're very effective at assisting in the diagnosis when emerging infectious disease events occur.

And this slide on the top shows an immunohistochemical staining for West Nile in the brain. Subsequently, there have been a number of dramatic examples of transmission. And you'll notice I'm sort of mixing purposefully comments about the blood side and the organ side of things to kind of cover issues that will arise today -- both today and tomorrow. But you'll remember perhaps the transmission of Rabies virus from an organ donor to four recipients back in 2004. An episode of Lymphocytic Choriomeningitis virus transmission by
organ transplants in 2005.

Again the pathologist coming into play with providing evidence of Rabies virus infection of the CNS and Lymphocytic Choriomeningitis virus, LCMV, in recipient tissues in the other event. And then the source of this LCMV cluster of infections was this little Syrian hamster; keep him in mind, we'll come back to him.

Even more recently a new Arenavirus in a cluster of fatal transplant associated diseases. This represents work of CDC and Dr. Ian Lipkin among others from the Mailman School of Public Health at Columbia, but allows me to remind you that pathogen discovery is very much a part of this arena and I think we'll probably hear some more about that this afternoon.

And then another fairly recent event of transplant transmitted tuberculosis. Now to get even more exotic, recently, there was attention given to this event involving Balamuthia mandrillaris, an organism that may not be on a whole lot of people's radar screens here, but it was initially discovered back in 1986 by some people working with tissue from a mandrill baboon from the San Diego Wild Animal Park. But this is a severe infection of
the central nervous system. And a recent transplant associated transmission event occurred, and again, the pathology community came to the rescue with the diagnosis.

Dr. Epstein mentioned XMRV which has recently surfaced. This gets at the role of microbes in chronic diseases, and you know, the report came out that XMRV appeared in one initial study to be associated with chronic fatigue syndrome. Now subsequent studies are continuing. That association needs to be worked out and either confirmed or set aside, but it obviously has potential implications for the blood and organ transplantation communities.

Some of you may have seen a very recent report in the MMWR of transfusion related transmission of Yellow Fever vaccine virus in a setting where people did not defer blood donation for the recommended period following receipt of Yellow Fever vaccine.

And Dr. Epstein mentioned the ongoing Q fever outbreak in the Netherlands which began back in 2007 and continues, and is anticipated to continue for a while longer and you can see from the epidemic curves there in 2007, 2008, 2009 that obviously the problem has been
increasing.

So here are two very important papers that I'm sure are familiar to most of you in the room. I have to say in getting ready for this talk, I had not seen them and Dr. Kuehnert kindly called them to my attention. Thank you, Matt. So I've looked at them and I look forward to hearing much more about them later today and tomorrow.

Now, on the international side, thinking about surveillance, there are some opportunities. The World Health Organization in 2005 issued the revised international health regulations which updated and modernized the previous version that had been issued in 1969. And for the sake of time I'm not going to get into a lot of detail here, but they call for timely reporting information sharing. This transparency and exchange of information that frankly did not occur with SARS, at least through the first several months of the SARS epidemic and led to some of the geographic dissemination that occurred that potentially could have been prevented by earlier reporting.

They also emphasized the importance of
laboratory capacity. We're going to be talking about laboratory capacity in the U.S., but I think we need to remember the situation with laboratory capacity or lack thereof in much of the developing world.

So the goal of these is to prevent international spread of disease. They're not a surrogate for national surveillance and response systems but they do require -- this is an international treaty signed by all WHO member states. And the treaty requires them to be able in a timely way to detect, assess, report, and respond to public health risks and emergencies of international concern. So there is a lot of work to be done in this arena.

The regulations provided a decision instrument for countries to use in assessing whether or not a particular disease event represents what they call a public health emergency of international concern or a PHEIC of all things. It does require immediate notification of even one case of smallpox, polio, SARS, or influenza caused by new subtypes.

And then the notification of a number of other diseases based on use of the decision instrument to make
an assessment of the potential international relevance of a local disease occurrence. Now let's come back as we're getting near the end on the zoonotic disease arena.

Dr. Lonnie King who is now dean of the Vet School at Ohio State, but back when he was dean at the Vet School at Michigan State wrote this. "We have a new world in terms of the epidemiological convergence of animal health and human health. It's an epidemiologic collision."

Reviews -- and I'll show you examples of a couple of those in a moment -- but recent reviews in the literature have concluded that somewhere between two-thirds and three-quarters of recent important examples of disease emergence or reemergence represent zoonotic disease events.

This has led to a so-called One Health Initiative movement. One Health, when you hear about this, what people mean is the convergence of human health, animal health, and ecosystem health. So it fits, it is a large part of the bigger emerging infections agenda but it fits right in there and it includes early detection before transspecies transmission, and an extension of it even
includes dealing or trying to address some of the root causes that lead to these cross species transmissions.

Now, here are the two papers; you can see them probably better in your hardcopy of the slides, but the references are there if you're interested in looking at them. Let me just ask, and I always like to do a survey now that I don't have to worry about OMB anymore.

How many people in the room have a DVM degree or training in the veterinary world? Just out of curiosity. I see about three, four, five, six hands, okay. This is what usually happens at meetings. Sometimes if I'm speaking to vets I ask how many are medically trained and you see, you know, typically relatively few hands.

I think those of you concerned about blood and organ and tissue safety need to get to know your veterinary colleagues a little bit more. The pathogens are trying to tell us that. It's been pointed out that there are, in terms of where new diseases emerge, there are potential hotspots, rain forests, hot reservoirs or hot species bats, pigs, and prairie dogs, particularly recently, hot settings the wet or live animal markets, hot vectors Aedes albopictus, the Asian tiger mosquito, and
hot vehicles bush meat comes to mind.

Climate change isn't going to help and we've talked about the need to improve preparedness and response, and I just mentioned a few of the lessons learned from these recent outbreak experiences. The importance of strong national and international partnerships we talked a little bit about that. The increased multidisciplinary or some people even say trans-disciplinary collaborations including human and animal public health sectors.

Health system strengthening including public health lab capacity; transparency and political will in fighting this complacency; the global commitment to addressing inequities; the importance of strategic and preparedness planning and that's some of what we'll be talking about the next two days. Developing research agendas, very important, Dr. Epstein alluded to that; addressing training and education priority is very important, and then finally, facilitating proactive communication.

So what does the future hold? This slide used to just say influenza pandemic. Now we have to say
another influenza pandemic since we have just experienced one, stay tuned.

Antimicrobial resistance, we've haven't talked about that specifically but that's a big part of the emerging infections agenda. International food borne disease outbreaks; the possibility of urban Yellow Fever being introduced -- reintroduced in Latin America or introduced for the first time into Asia. Microbial etiologies of chronic disease, additional associations will surely be identified as the future plays up; when that happens, obvious implications for the blood and organ tissue supply.

And then finally, we know we have to continue to expect to deal with the unexpected. So the 2003 IOM report left us with a thought, "A robust public health system in its science, capacity, practice, and through its collaborations with clinical and veterinary medicine, academia, industry, and other public health and private partners is the best defense against any microbial threat."

So in conclusion, we talked about the trends that impact on disease emergence and reemergence. And
thinking about those I think you'll agree that most -- the trends in most of those factors in fact do favor the microbes. New threats will emerge; many will likely be zoonotic. Anticipation of potential threats to blood supply and risks associated with organ and tissue transplantation is very important and we'll be talking about that.

The need for health care and public health system strengthening is apparent to all of us, I think, and the need for vigilance, sustained political will, better predictive capability, improved coordination and communication, and multidisciplinary partnerships is critical.

So we're not going to be complacent, right? If you want to keep up with these events, I always like to put in a plug for one of my favorite journals Emerging Infectious Diseases, free and available online that contains timely reports on these issues in addition to what appears in the Morbidity and Mortality Weekly Report, the WHO, WER, and a number of other publications.

And last but not least I would like to invite you to consider -- if you aren't already planning -- to
attend the international conference on emerging infectious diseases which CDC is hosting and the program has been developed in collaboration between CDC, ASM, IVSA, the Council of State and Territorial Epidemiologists, and the Association of Public Health Laboratories, and WHO.

So we hope to see many of you in Atlanta in July, and that I think we can assure them that there will be a number of issues related to blood, organ and tissue safety on the program. He is nodding an enthusiastic yes. So thanks very much again. Thanks for the invitation. I'm looking forward to hearing the discussion over the next 2 days. Good luck with this very important and timely session.

(Applause)

SESSION I: IDENTIFICATION, SURVEILLANCE, AND PRIORITIZATION OF EIDs

DR. KUEHNERT: Okay. Thank you very much for coming and to Dr. Hughes for the keynote address. We're going to start Session I which is the identification, surveillance, and prioritization of EIDs.
And we're going to start with presentation by Marta Gwinn. She is a medical epidemiologist with the Office of Public Health Genomics at CDC. Her background includes laboratory based surveillance systems and research studies and CDC's HIV AIDS program and her current work focuses on integrating human genome research data for population level interpretation application.

I -- this really gets to something that I think is underappreciated which is so called horizon scanning and we look forward to this presentation. Marta.

HORIZON SCANNING: EXAMPLES FROM GENOMICS AND EIDs

DR. GWINN: Thank you. Well, thank you, Matt and thank you to the organizers for including me on the program where I really am something of an outlier. I actually was involved with blood safety study but it has been more than 10 years ago. And so what I plan to do today is discuss the issue of horizon scanning from the perspective of my current assignment which is in the Office of Public Health Genomics at CDC and then try to draw some potential parallels to examples for horizon scanning for emerging
infectious diseases.

And I guess I'm somewhat encouraged that some of my examples have already been touched upon by previous speakers that suggest that I put on some of the important ones. And I'll show you some ways in which interest in those as reflected currently online and in the media. So I have to add my disclaimer, which is that my comments have not been formally disseminated by CDC, ATSDR, and should not be considered to represent any agency determination or policy.

So what is horizon scanning? Well, I believe that this term has become popular in government largely since about 2004 when it was used by the Chief Scientific Adviser's Committee in the United Kingdom in a report on planning for the future. And basically, what it means in our context is the systematic examination of potential threats, opportunities, and likely developments and the ability to detect novel and unexpected issues or persistent problems and trends.

And one thing that I think is kind of interesting is that with all the current emphasis on evidence-based medicine, it's important to think of
horizon scanning as sort of a flip side in which evidence synthesis, the process of evidence-based medicine looks back at experience and horizon scanning looks forward to see what might happen.

So as I mentioned, I'm going to talk mainly about experience that we've had in looking for genomic research applications and then try to draw some examples for horizon scanning for blood borne emerging infections. So what are we doing? We're trying to find and track epidemiologic data on gene disease associations, interactions, and genomic tests, and here I'm talking about the human genome.

Our sources are scientific literature, news, also industry websites are an important source, and we use a combination of automated and manual processes. And what's our public health interest in this? Well, there is two sides really. One is to anticipate the public health implications of premature translation; in other words, the rush to market without sufficient evidence and the problem of lost in translation in which potentially promising applications somehow go off the tracks and never make it to the people who might benefit from them.
So some of the challenges in this field are that -- that basically there is too much information and it's coming out too fast. And it becomes something of a needle in a haystack problem to find what's really important and what is pertinent to public health interests. The sources are very heterogeneous and so are the channels in which the information is disseminated.

Also there is a wide range of content, it's hard to classify. Many dimensions, for example, there is human genomes also mentioned previously, pathogen genomes, there is health data, there is a lot of complex research data. And there is also a major disconnect between the producers of a lot of this information and people who might actually want to use it.

There are some advantages in this field though and that is, for example, that there are major incentives for publication; not to mention publicity of important new findings and there is a large and avid group of consumers so there is a great deal of media interest in spreading the word. So this creates something of a feedback loop that keeps the information flowing.

So I'm going to briefly describe just three
approaches that we have to horizon scanning for these genomic research applications. One is the scan of scientific literature for relevant gene -- genetic associations, gene environment interactions, systematic reviews and meta-analyses and so forth.

Another is the news and media for discoveries, inventions, ventures, products, and clinical studies. Also broader topics like practice guidelines, ethics, issues, costs, health outcomes, et cetera. And then finally, the industry pipeline which is the best place we have found to look for tests that are under development that have been launched or been licensed and are being evaluated.

So first on the scientific literature. I'm going to mention that on each one of these dimensions, we actually have created an online vehicle to provide the information to users and the public along with some tools for searching it, and I'll start with the scientific literature where we've developed the HuGE navigator.

We have a weekly online update that captures significant news stories and then we have a new online application. You can see it's a beta version of what we
call the GAPP Knowledge Base that allows you to search for information about genetic tests.

Okay. So first, the scientific literature. Well, if you look at PubMed, for example, the amount of annual publications on human genetics has just grown rapidly and I'm only going back to 1995 here when they were already 30,000 articles that one could turn up by simple PubMed search. And in 2001 is when our office systematically began extracting from PubMed in a systematic way. The articles or citations that meet our definition of human genome epidemiology, which is basically studies of human genetic factors in populations or groups of people that would be as opposed to pathologic studies, molecular studies, and would exclude the animals also.

So we started out with PubMed query that everyone is familiar with and it was a complex query because it had to capture multidimensional information. In 2001, this is what it looked like and as we continued and found that we were missing certain articles, our curator began to enhance the query and it soon became over 3 years this -- unwieldy mess. I mean it was very complex
and it was also very nonspecific. Our curator developed bilateral carpal tunnel syndrome.

So this is the tactic that we took after realizing that the classic query was not going to work for us. My informatics colleague Wei Yu has developed an approach that depends on artificial intelligence. It's basically a machine learning approach that uses a support vector machine to screen PubMed weekly, and basically this approach has reduced the volume of literature that has to be hand searched by the curator by 90 percent.

The curator then selects an index as the articles and we also use auto-indexing facilities that are available through controlled vocabularies, and for example, places like Entrez Gene, MeSH, and Unified Medical Language System. And then we -- as I said, we've created the web applications to sort, filter, and display the data in ways that users can search it and that's the HuGE Navigator which the URL is there. There is also an article about it in *Nature Genetics*. And this is what the main page of the HuGE Navigator looks like and I'm just going to show since this is not directly applicable to your interest. I'm just going to show an example of what
you can do with it.

Using this particular tool, which is the Genopedia, and here I have searched for the gene for the Duffy red cell antigen or DARC, and there are 25 publications in the database and you can see here disease associations that have been reported. There haven't been any meta-analyses, genome wide association studies, et cetera.

Those are important and some other areas and I want to show how using these control vocabularies makes it easy to connect this database with others. For example, at the gene level, one can go directly from this site to all these other sites that have information on this gene including general information. You look up their specific searches and other gene-based databases as well as pathway databases like KEGG and so forth. And you can see down here where some of those links go including to specialized databases like the PharmGKB for pharmacogenomics and OMIM which is Mendelian disease database.

So next to the news and media. As I'm sure you know, there are many different news aggregators, and Google also provides an alert facility that you can
actually request an alert on any topic of your choice with a frequency that you choose as well. So an example, I mean, I get this alert every day which is a very broad alert for genetics and here you get a whole variety of different kinds of stories, for example, this is on gene-discovery of an association.

This is translation, basically using information about Crohn's susceptibility factors to try to tailor treatment. This is of course about zoology, this -- many different applications of genomics. And this is an online newsletter that our office publishes weekly with selected excerpts from these news stories and other -- they use other alerts as well, and they cover a wide variety of different things and some of them are grouped by diseases, for example.

Okay, so finally I'll just talk briefly about our newest approach which is looking at the industry pipeline. And here I have a Google news search for just the simple term "genetic tests." And as you can see it turns up a lot of really, you know, not very scientific things, including the sponsored links AABB, Accredited Paternity Test, all right.
So -- but there are you know -- there are, even within this thing -- some things of potential interest for example down here, we see under this transplant story some related stories that there is a company that is seeking a label change for transplant rejection test. And here is what the -- you know, clicking on that link takes you to this source, which is actually one of the best. And it just says, here is a gene expression test to determine whether heart transplant patients are experiencing rejection.

And this is the website where we're trying to pull some of these things together including the news stories and updates on the latest genetic applications added to our database which is GAPP finder which I'll show you in a second as well as recent publications.

And as I said, we just started doing this. The genetic test search goes back to the middle of last October and it is updated weekly. Right now we have about 159 genetic tests in there. And so this is the tool for searching the tests and this is kind of what it looks like if you just display all of them. So it's really only very basic information, but it's sort of a monitor of what is
actually coming out of the pipeline.

And another thing that we're doing is this what we're calling the evidence for genomic applications, and this is being published online using a platform that Google developed called the NOPHG, a unit of knowledge, and here people will be able to submit and publish and get direct object identifier and their article indexed in PubMed Central for brief summaries on the validity and utility of genetic tests.

And in doing this we've modeled it on PLoS Currents Influenza which you may have seen, which was sort of an experiment to make use of this platform in order to publish rapidly breaking research notes. And it has been successful, and we're actually in communications with them. They gave us a lot of help in setting this up.

So now, I'm going to talk just briefly about my ventures into the arena of blood borne emerging infections. And I was thinking that the idea would be to find and track relevant research findings, incidents and outbreaks in published literatures such as case reports, news and surveillance systems, again using automated and manual processes to anticipate emerging infectious threats.
to the blood supply.

So one thing I looked at here is the scientific literature where actually in, it just says "Blood transfusion and infection." And in PubMed you can request case reports, and so doing that I found this case report, which you can read online. And it's a report of a case of Babesiosis, which was mentioned, and there are the details of the case.

You can also see that this was received for publication in September, revised in November, and published online immediately after, and here is a print version in February. So this is not extremely speedy but it does provide a lot of documentation of the case. Here is a Google News search for just the term "infected blood," and this also provides a whole variety of different kinds of things.

Here is an outbreak. It's the Rift Valley Fever outbreak. Here is some news about a diagnostic test for Chagas disease. There is a report of an incident here this one was in India. And then there is always a lot of celebrity news on Google, so it's hard sometimes to filter out the chaff.
Now, for a month I ran this Google alert, "infected blood," and I limited it to 10 items per week. And there weren't 10 every week, but you can see that overall, really a minimum of them had a small number, maybe on the average of two per week had something that I felt might possibly have to do with blood safety.

Most of the rest had to do with infectious diseases of one kind or another and then the ones in green were unrelated and actually a large proportion of those had to do with the movie called Crazies in which infected blood causes an outbreak of rage, and I don't know, had to screen through all those.

So what did we find in that month, well the largest category was policy, and an example of that would be reports on Australia reviewing its regulations on beef imports and donor deferral. There was something from the U.K. about filtered blood transfusions for children. And again, U.S. reconsideration of deferral of gay and bisexual male donors, and that was actually a big topic during that month because there were some public statements by senators and others and so there were actually 10 items related to that was most of that
category.

The law was the second largest category and there was a bill in the U.K. parliament having to do with compensation for people infected through transfusions that was a big item. General topics were more like health education, explanation of these different conditions and how they could be transmitted by blood. There were reports of a few events.

There was some - this, I should mention this one here, this is blood contaminated with Yellow Fever vaccine, was still news from an incident that had occurred the prior year. And then you can see there is some other incidents from other countries in the world.

Technology, there were several of these including development of technologies that could be used in the field or potentially as point of care diagnostics, and then there was historical articles. So ProMED mail was mentioned and this is -- it's still a very important resource for us, information on emerging infectious diseases, and it was founded in 1994.

So really it was kind of ahead of its time and first these e-mail and you can subscribe to e-mail alerts
but also has website, so just taking a look here at this particular -- I searched here for "transfusion" and these are the results.

Yeah, so that's the number that we got and this is going all the way back to the beginning of 2010, so there were only a few, and I just made them larger here so you can see what they are. There are monthly updates on Prion disease so that you see those there, and there are several other ongoing stories including the one of Q Fever that we just heard about.

And I'll show you this -- the story here which links to the eurosurveillance.org website where you can see, you know, the Dutch surveillance data including their map, pictures of affected goats and so forth. As well as a link to the surveillance database that shows the epicurve, which I think you saw another version of this in a publication but this has been updated and it shows much, much lower incidence in 2010.

So where does transfusions fit in; in this report there is a comment on the theoretical risk of transfusion and on the steps taken by the organization responsible for blood products in the Netherlands which
started screening in high incidence areas of the country on March 15th; so that was about a month before I ran this.

What about Google Trends? Everybody has pretty much heard by now about how Google Trends could have identified influenza epidemic earlier than CDC, MMWR, and so forth, and there has been a number of articles published in Nature and other journals about the use of the Google search engine to monitor trends in actually user searches for specific terms related to influenza and using that information to detect outbreaks. So this is one of them.

Here is a Google Trends search just on the term "transfusion" going back to 2004 which is when they started this facility, they first made it available. And I have not been able to figure out how they identify these points and how they associate these stories with those points, because for example, I was unable to find what this reflected. You can see here, this is news volume.

Obviously, there was a big news story in the middle of 2007, but I was not able to determine what it was from this site. Also some of these stories do not
look like they would have generated a lot of searches, and so I really don't know how they do that. Also I thought it was interesting though to see where this particular search was most popular, Maryland, maybe it was Gaithersburg.

(Laughter)

DR. GWINN: -- or Rockville, yes. Okay, so here is a recent article from clinical infectious diseases about using Google Trends for surveillance of outbreaks, and you know, one of the author's conclusions is that although this tool shows great promise for surveillance it is probably best for surveillance of epidemics and diseases with high prevalences. So if you're searching for a needle in a haystack, it may not be as good as say, looking at Flu Trends.

And here it also mentions that it may be better used in the developed world where many, many, people have access to the Internet, but I, you know, I think that is actually changing. So here is sort of the next generation beyond ProMED, some of the same people are involved and you will see over here that this particular project, HealthMap global disease alert incorporates information
from some of these sources that I've been talking about including Google News.

There is a wildlife disease note, so this is a veterinary surveillance system. There is ProMED which I just mentioned, eurosurveillance which I linked to, and there actually are others as well. And here people, individual alert clinicians, alert veterinarians, alert laboratorians, alert members of the public actually can make reports through this system.

And I mean this map has got too many things on it to be able to look at, but if you click on the little icons you can get details about what's going on in each of those areas. Oh yea, I just showed that.

Now this is an article and really for a single paper explaining the use of these kinds of tools and how they have developed in the last few years, I think this is the best paper that I could find, and this author John Brownstein is involved in the HealthMap project, and this explains how some of these different initiatives fit together as well as how they evolve from very early efforts like ProMED mail, and also this global public health intelligence network that was established in Canada.
very early on, so the article is about 1 year old.

This is a figure from that article, and if any of you remember the Salmonella in peanut butter outbreak from last year, you might be interested in seeing this. I mean, as you might expect, after the public announcement of this problem is when the searches really spiked including searches for peanut butter, searches for Salmonella, and searches for recall. But there is a time before that when these searches for food poisoning and for diarrhea actually showed an increase.

And so you know there is many interesting research questions and opportunities for analysis and potentially for fine tuning this type of a search capability for -- as basically an early warning system.

And this actually just came out in the last week or so and it's -- I added it just to show that, you know, this is a very active area of research. This one is -- this paper is actually commenting on another system called BioCaster. So there are a lot of different models out there in a lot of research right now.

So just a few concluding thoughts I guess. I was only guessing at what the objectives of the horizon
scanning might be, but obviously, the type of scanning that you do depends on the objectives whether it's to detect sentinel events or possible events or to describe ongoing events.

So another factor in determining how to guide the scan is what really are the essential qualities, is it timeliness, do you want really unbiased information, does it need to be validated and so forth.

There are many existing systems that can be used for horizon scanning, and it would be interesting to really do a systematic exploration of those to see which ones might be most useful and pertinent. Search strategies can be tested and evaluated. And in that machine learning example I described we actually did very, very extensive evaluation of its performance characteristics before we actually replaced the old system with the new one, and we ran that in parallel for 3 months and that's why I could say that it actually reduced the, well, it improved the sensitivity by a tremendous amount because it reduced the number of searches by 90 percent and we did not lose any sensitivity.

One thing is plan ahead for sharing, and I
showed some of the online systems that we created to allow people to access the information, but I think the main reason for sharing is because users can add value as in the HealthMap members of the community can report. It becomes more of a dynamic information platform and not just one way dissemination.

And finally, the integration of the objectives with those of like-minded communities, I mean similar to what Dr. Hughes just mentioned, joining forces with the veterinary medicine world and so forth. And I just want to acknowledge some of my colleagues in the office including Anja Wulf who is the frontline horizon scanner. We have subject matter experts who serve as curators and Wei Yu is my informatics colleague. Thank you.

(Applause)

Q & A

DR. KUEHNERT: Thank you, Marta. Are there questions for Dr. Gwinn? We have time for a couple of questions. I think this is something that is not at the forefront of many peoples' minds in this area. I think
there has been a lot of focus on research and as most -- some laboratories, some epidemiologic, but you know in terms of horizon scanning, I think it's very important.

When I think about how we have found out about outbreaks that are of concern to blood safety it tends to be colleague or a well publicized publication where the work has been done months if not years before. So one thing I wanted to ask you, you talked about validating search terms, you know, looking at blood, you are going to end up with a bunch of results on vampires probably.

So you know, I think transfusion or transmission gets you a little closer but how do you start with the validation process? Do you start with a well-known paper that has defined search terms or do you use focus groups? I mean, how do you sort of start?

DR. GWINN: Okay. Well, the place where we've really done that validation was in the scientific literature which is obviously much easier than say trying to look at news headlines or something, because those are ephemeral, you know, many of them disappear and so forth. But in the scientific literature we have the wonderful resource of PubMed which, you know, basically is an archive
and what we had is -- we had a body of citations from the
first 5 years of laborious hand curation that served as a
training set for our support vector machine.

So we actually trained this machine on a set of
existing literature, and then turned it loose prospectively
while we continued our hand searching for 3 months and then
we compared the results. And you could do the same thing
for say transfusion safety or whatever. If you have a
bibliography or a set of literature that you say
represents the key, you know, the essential literature or
may be the comprehensive literature on this topic and then
you could train that and you could do it prospectively.
You could do the same.

DR. KUEHNERT: Thank you very much.

DR. GWINN: Thank you.

DR. KUEHNERT: There is a question?

MR. TIBBETTS: How would you see this approach
being used to glean out some information on host pathogen
relationships with the massive information on human
genomics and also on infectious disease trends?

SPEAKER: Please identify yourself, please.

MR. TIBBETTS: I'm Clark Tibbetts; happy to be
DR. GWINN: Well, thanks for that question. I'm really interested in that topic myself also, and one thing is that we can use our HuGE Navigator which I showed you the tool that's based on PubMed citations actually, to do a little bit of that. Because that's -- the focus of that system is on host genetics. So you can actually search our system for an infectious disease of interest, say, malaria, for example, and find all the epidemiologic studies that have looked at host genetics in relation to that particular disease since 2001.

Now, some of them -- there is very limited information like -- I didn't actually try putting Babesiosis in there but there may not be anything or there may be very few. But for the big infectious diseases, you know, there is a substantial amount of literature in there, so that would be one place you could actually start on that.

Now in terms of host genome versus pathogen genome, that is a subset of that and that would be an interesting subset actually to identify. I mean that would actually be a good project to work on, and I think it would
be interesting. So thanks for the question.

DR. KUEHNERT: Great. Thank you very much.

DR. GWINN: Thank you.

DR. KUEHNERT: My co-moderator Dr. Nakhasi will -

REPOSITORIES PERTINENT TO TRANSFUSION SAFETY

MR. NAKHASI: Hello -- all right. So I think in
the interest of time and the theme, I think the next step
-- next stage in the theme is the surveillance. And I
guess -- you know, the speaker for this session is Dr.
Steve Kleinman. Dr. Steve Kleinman is going to be talking
about repositories pertinent to transfusion safety, Dr.
Kleinman is a -- currently a senior medical advisor to
AABB, and a clinical professor of pathology at the
University of British Columbia. He also operates a
transfusion medicine consulting company.

His past professional experience include medical
director of a regional blood center, the American Red
Cross in Southern California, medical co-director of
transfusion services in UCLA's Medical Center, and has
been an investigator in several multi-centered transfusion medicine research studies, including ongoing NHLBI sponsored retrovirus epidemiology donor study, in short form REDS.

His main research interest has been transfusion safety particularly assessing and preventing infectious agent transmission. He has published a lot of papers, and a lot of book chapters. And so with that, I think, Dr. Steve Kleinman.

DR. KLEINMAN: Thanks Hira, and thanks to the organizing committee for inviting me to speak today. Well, from this massive global overview that we just heard, I'm going to really focus down on a very specific topic, and that's repositories pertinent to transfusion safety.

So in the time I have today, I'm going to review the characteristics of the current repositories, review selected results so you can get a sense of the usefulness of these repositories, describe the current way that investigators can access the repositories, and speculate on their usefulness for new agents which I think will be ongoing during the course of the morning and the
afternoon.

So, I'm going to focus primarily on repositories that have linked samples from blood donors, and recipients who received transfusions from those donors. The purpose of these repositories is that they allow for the evaluation -- in the context that we're discussing today -- is that they allow for evaluation of transfusion-transmission of known and future agents. So -- but they have some limitations as well; they can provide a time-specific snapshot, obviously, the repository is collected over a specific time period and so you can find out what was happening during that time period. If however, you get an agent introduced in the blood supply subsequent to collection of the repository, the repository won't be useful.

They may also be limited by the geographic catchment area in which these samples were collected. We have an example here; our repositories weren't of much use for West Nile, because they came from communities that weren't part of the major epidemics. And I think, most importantly, we can determine the transmission rate of a new agent with some confidence, however, if we're looking
for very rare transmission events, and we wanted show that their -- they don't exist, then there's a little bit more difficulty in the statistics.

And I think one thing to keep in mind is these don't get put away too often because enrolling recipients and their corresponding -- and collecting their corresponding blood units is expense -- it's logistically difficult and very expensive.

There are three large-scale linked donor-recipient repositories in the U.S. that I'll talk about in some detail. One is the Transfusion-Transmitted Virus Study or the TTVS, the second is the REDS Allogeneic Donor and Recipient Repository, which has the acronym of RADAR. And the third is the Transfusion Related Infections Prospectively Studied, only Harvey Alter I think could come up with this name -- this acronym, but TRIPS, which is an ongoing study that I'll mention briefly.

There are also other recipient-only repositories, one is FACTS, frequency of -- I don't know -- well it's FACTS anyway, the acronyms are easier. And donor-only repositories from the TSS and REDS, and these are illustrated on the next slide in some detail; the ones
in blue are the linked-donor recipient repositories that I'll concentrate on it in the next little while.

And just to go through them briefly here, the TTVS was a very old repository put away at the end of the '70s. As I said, it's a linked-donor recipient repository. The sample type that's in the freezer is serum. There are -- there were about 5,600 blood donations put away from -- and 1,500 recipients who received these donations. The major agents that have been studied are the hepatitis viruses, particularly HCV and HBV. The RADAR repository, as part of the REDS study, was put away from 1999 through 2003. This repository has both plasma and frozen whole blood samples, which can be used to access cellular material, and therefore do nucleic acid testing. There are 13,201 donations that are linked to 3,574 recipients; the only agent that's been studied to date is parvovirus B19.

The TRIPS study began in 2001, and is still ongoing. Again, a linked-donor recipient repository plasma and frozen whole blood. About 6,000 donations and 1,000 recipients at this point in time, and ongoing studies for the agents that are listed here, HHV-8, CMV,
EBV, and parvovirus B19. There's an older repository collected by the NIH Clinical Center, it went on -- these collections went on for decades in which serum is stored, and you can see there are about 30,000 donations and 3,500 recipients, again used to study many of the hepatitis viruses and some of the new or potential hepatitis viruses.

The VATS study, viral activation from transfusions, was a study in HIV infected patients to see whether their HIV infection would get worse with transfusion. So it's very specialized repository of 531 recipients, but it's been used to look at the occurrence of many agents in this population.

The FACTS study, from 1985 to 1991, collected recipient samples, has stored serum from 11,494 recipients, and has been used to study a multitude of agents; HIV, HTLV, HCV, HHV-8, and T. cruzi. The transfusion safety study, again from the mid-80s for 2 years, is only a donation repository, no recipient samples, the specimen type is serum, they're over 200,000 donations, main studies were HIV and HTLV.

And two repositories put away during the
retrovirus epidemiology donor study, from 1991 through 1995, originally serum, and then subsequently plasma and frozen whole blood. You can see a huge number of donations were put away, over 500,000 serum samples, close to 150,000 plasma and frozen whole blood samples. And these have been used to do a small sub-study -- small sample sets within these repositories have been used to look at HBV, CMV, and HHV-8 donor prevalence.

Now, just a couple of general points from this slide, you'll notice that the size of the donor repositories are much larger than the size of the linked donor-recipient repositories, again, I think, illustrating that it's not so hard to put away extra blood from blood donors, but if you're going to link those to recipients it's a much more logistically complicated and expensive task. So you can't put away as many samples. Again, I think you'll see that, and you can see that the -- even the recipient repository -- the FACTS study that didn't try to link it with donation samples has considerably more recipient samples than any of these linked donor-recipient repositories.

So I want to talk mostly about the donor-
recipient repositories, and this may be a little bit biased because I'm going to talk more about the ones that I'm familiar with, and that will be -- so it'll be a little bit more on the RADAR repository, and then some on the -- one of the donor-repository is a transfusion safety study.

But anyway, returning to the TTVS, its specific purpose, the study and the associated repository list to study non A, non B hepatitis transmission. It is a multi-center study done in four regions in the U.S. These samples were collected at a time, in the late 1970s when compared to today; transfusion-transmission was most likely maximal.

There was much less extensive donor behavioral screening, there were many fewer donor screening assays, the majority of the units transfused back then were whole blood transfusions, so no leukoreduction and large volumes of plasma, again maximizing transfusion. In fact, some of the regions even used some paid donors. Again, a good way to maximize your transfusion-transmission, and there were a large number of transfused units per recipient.

Now, this repository has one unique feature in
that it recruited a control group of surgical patients with similar diagnoses to the transfused group and so -- but they weren't transfused. So there's actually -- you can look for the frequency of agents in hospitalized patients with similar diagnoses, and therefore be able to make, I think, some more valid conclusions that that transfusion was actually the ideological agent in the transfused group.

Specimens were collected quite frequently so that from recipients there was a pre-transfusion sample, and then samples were collected at 2 to 3 week intervals, all the way out to 6 months post transfusion.

Now, all donor units transfused to the recipients were included in the repository. So if a cardiac surgery recipient got eight units, then there were samples from all eight donors put away. Well, I'm sure there were some exceptions, but that's true in the large majority of cases.

While the limitations of this repository that is clearly not useful for agents that weren't around prior to its collection date, which is now a long time ago, 30 years ago, specimens and currently many of these specimens
have been used extensively and therefore some specimen groups may be nearing depletion. Thirdly, the specimens were collected prior to anybody conceiving of PCR or NAT testing, however these samples have been accessed for NAT studies and although not optimally collected perhaps for this purpose, they seem to have been adequate.

However, I think you have to ask whether if you had a very sensitive agent -- if you had an agent that was present in very low concentrations and you needed to really have a sensitive assay to develop it, whether the sample quality here would be sufficient. And I don't know the answer to that. Now, lots of contributions from the TTVS in the first decade, when it was put away, studies were done on the risk of non A non B hepatitis, which again was its primary purpose.

And then the repository was used to evaluate the efficacy of surrogate testing, meaning ALT and anti-core testing, and then eventually anti-HCV EIA testing. Then in the second decade, these samples were re-accessed for HBV transmission studies, and were able to provide some additional information on the utility of core testing for HBV, and then other agents were begun to be looked at --
HGV/GBV-C, the main example.

And then the third decade, really more sophisticated studies were -- began to be done with these samples to look at the viral dynamics in early HCV infection, to look at donor and recipient factors that might be associated with transmission. These samples -- these recipients actually were -- the identity of the recipients were accessed by Leonard Sepha (phonetic), who in his long-term outcome studies was able to use this and other studies to look at what happened to people 20 to 30 years after HCV infection. Some more elaborate work done on GBV-C and TTV transmission, and even an HHV-8 transmission study was just published a couple of years ago using samples from this repository.

So I just want to show you a couple of data slides here, this one shows the ability to look at HCV RNA levels, and correlate it with whether in the donor units, and correlate this with whether or not the -- there was seroconversion or acquisition of an infection in the recipients.

And as you can see here, there were some seroconversions that occurred with very low HCV RNA
levels, and a few, lack of transmissions by RNA positive units, mostly -- well at least by two RNA positive units. So I don't want to get into the details, but to show you the kind of studies that can be done. Here's another viral dynamic study, in which you can see the time to development of these markers in the HCV infected recipients, and this information is well known, but obviously RNA was detectable prior to ALT elevations, prior to antibody development.

So I'm going to switch now to a second repository, this is just a donor repository, but I think it gives us some interesting insights into the kinds of studies that can be done. So this was a transfusion safety study, its specific purpose was to study AIDS, and it was originally conceived at a time prior to the identification of HIV.

It was done in four geographic locations, basically the big cities that had the highest incidence of AIDS. And although a recipient repository was not established, the reason I've included this is that as positive donor units were identified, the recipients were identified in those cities and were tracked and enrolled,
and studied. So although there wasn't a primary donor recipient linkage, there was kind of a secondary method to do that.

So this repository was valuable in that it established the rate of transfusion transmissibility from anti-HIV positive components, which was at a rate of about 90 percent, correlated transmission with viral load and age of the units, I'll show you a slide on that. It was accessed to do a very targeted study of HIVp24 antigen yield; I'll show you a slide on that. And that's published there. And then subsequently, was actually used for more sophisticated molecular biology studies of HIV transmission clusters, and the studies of HTLV transmission.

So, this slide which is a little difficult to read I think, but if you look at the open white dots, these are units that -- red cell units that did not transmit, and they seem to be units that both had lower HIV RNA viral load and were older in their storage period, above 20 days. The statistics on this are a little bit weak, but they do at least tell us that in the cases of non-transmission maybe red cell storage based on viability
of surviving -- HIV surviving in viable lymphocytes may be a factor that contributed to the lack of transmission.

And then this, I think, interesting study -- if you could find my mouse I could point here, yeah. Sorry. So, here at the time HIVp24 antigen was initially being considered for screening of blood donors, two studies were done, a prospective study on HIV antigen but a second study here on accessing this repository.

And the strategy was that because this repository was collected in areas with very high HIV antibody prevalence, one could actually expect to find more yield, because there was more HIV at this time. And rather than testing all the samples in the repository, one could go to zip code areas that had very high anti-HIV positivity rates in blood donors in 1984 and 1985, and select samples from the risk group, which were men in the sexually active ages of 18 to 44, assuming that's a surrogate for -- obviously males can have male sexual activity.

And so you can see here, if you look down at the total column here, in 73 zip code areas there were 9,000 male donation samples, and these -- this repository had
already been screened for HIV antibody, had an HIV antibody positivity rate of 1.54 percent, as opposed to the general repository of 200 -- of another 188,000 samples that had a very low HIV positive rate.

So the plan was to take these 8,500 samples and say, this is where new HIV infection would be found. We could screen only these 8,500 samples for p24 antigen and get information that could then be extrapolated through statistics to say what would have been the rate. And so in a very large -- in a very small amount of testing one could actually project that the p24 antigen yield, had it been applied to the current prevalence rate in 1994, would have been less than 1 in 2 million units, which in fact turned out to be true once we put p24 antigen in place. So this provided some kind -- a unique way to selectively access a repository.

I want to go on now to the RADAR repository. This repository was unlike the TTVS, which was put away to study a specific agent, the explicit purpose of this was to serve as a resource for the study of newly identified transfusion transmitted emerging agents. This repository was collected in four communities -- I'm sorry, over 4
years, in seven geographic regions which are listed here.

The recipient enrolment included a pre-transfusion specimen or one collected peri transfusion right around the time of transfusion, but unfortunately is limited by having only a single follow-up specimen, which was collected at an interval -- the aim was about 6 months but all the way out to 12 months, with an average of about 8 months after the transfusion.

The components from the RADAR donors, so the donations were collected -- and the way the recipients were identified is that these donations were specifically targeted to surgical patients on clinical services at hospitals who agreed to participate. Obviously, the IRB process in the -- in 2000 was, I think a little bit more administratively difficult than the ones back in the 1970s.

So you selected hospitals where -- and the patient population, the surgical patients, were selected to have no obvious immunosuppression and to survive for 6 months -- predicted survival for 6 months or more. So the specimen sources, what is in this repository is 13,000 donations linked to -- in recipients who were fully
enrolled.

And that means that they had both the pre-transfusion and the post-transfusion sample. But here, it was impossible because of the multiple sources of blood that hospitals used -- now they don't get all of their blood from a single provider -- it's very hard to put every donation away, and so in fact these recipients got both units that are in the repository and units that came from other sources. They average about four units from the repository and three outside the repository. Most of these are red cell units, 98 percent of the recipients got a linked red cell unit.

But if we look at the component types in general, 42 percent were leukocyte reduced red cells, 35 percent non-leukocyte reduced red cells, because different regions were handling their leukoreduction policies in different ways. Thirteen percent of the transfusions were from whole blood derived platelets that were part of the -- whose unit was part of the repository, and 10 percent FFP. But in addition, in order to be able to link recipients to these donation samples we had to put away many, many more donation samples.
So there's actually another 100,000 unlinked donations, without linked recipients. And then there were also 1,400 recipients who were initially enrolled who never came back for their follow-up sample either because they refused or because they didn't survive their underlying disease. In this repository there are two plasma aliquots of almost 2 ml each and one 1.5 ml frozen whole blood aliquot.

Now, the design goals for this repository were kind of different because we really put it away with the idea of saying, could we ever establish that a new agent is not transmitted by transfusion. How would we -- how do you prove a negative.

And so, while it's impossible to prove definitely the aim of this was to show that -- a given agent would not be transmissible by transfusion. Or if we translate that into statistical terms you can't really prove it's never transmitted, but we might be able to prove that its transmission rate is very low. And we took a target of 25 percent that we could prove that with a reasonable level of 95 percent certainty, and that led to the sample size calculations and the size of the
The secondary aim of this repository is if transmission does occur, to provide a measure of what the transmissibility rate would be. So -- now when would we access this repository? Well, we came up with a few rules, the first rule being that the question is of sufficient scientific or medical importance to justify accessing the specimens, that the donor prevalence was high enough to assure adequate statistical power.

And that an assay or assays with adequate performance characteristics, and that means basically sensitivity and specificity, but also could be done on small sample volumes, and had a high throughput where available.

And so the proposed testing scheme, which we actually used for the parvovirus B-19 studies were first to test unlinked donor specimens, these are less valuable because we have a lot of them, to validate the candidate assay, make sure it performed adequately, and to determine the donor prevalence. And then based on that, we could determine the power to actually look for transfusion transmission, and then once that was done, we would then
go into testing the linked donor specimens so we would know these are the positive donor specimens, we would see which recipient got those transfusions.

And then when we test the follow-up specimens from the recipients, and then if positive go back to the pre-transfusion sample to show that there was no preexisting infection. And we could do this on recipients of negative units as controls.

So we did this, as I mentioned, for B19 virus, we established the prevalence of B19 viremia or B19 DNA in donors. And we established the prevalence of B19 antibody in recipients because once you have B19 antibody you're presumably not susceptible. So you don't become a good candidate to evaluate transmission.

And then we determined -- based on these we determined whether we had power to do a linked transfusion-transmission study. We determined that we did, and went ahead -- and despite the huge size of -- I think, relatively large size of this repository, 13,000 donation samples, 3,500 recipients; we basically could find only 21 susceptible recipients who received positive units because most recipients by the time they're in their
60s have antibody, and we were able to show no transmission in this group which led to an upper 95 percent confidence interval of 13 percent. We focused on units we know that there's transmission if you have above 10 to the sixth international units per ml, so we focused on units that had less than 10 to the sixth.

And the conclusions were that it -- that we certainly don't have to do real-time screening if we have very -- at least for low levels of B19 DNA. And now we're -- there's another study that's been done which has actually taken these positive donation samples and looked to see what would you find if you look for DNA in the whole blood sample, since B19 virus has a predilection for erythrocytes and erythrocyte membrane receptors. And you can see here that this study, which was just completed shows that in -- at least in some phases of B19 infection you can find more B19 virus in whole blood than you can in plasma samples.

And we made a ratio of whole blood to plasma. You can see in this, higher viral load IGM positive phase, which is not shown on the slide, but that they're IGM positive but that the ratios can be much -- there can be
much more B19 virus in whole blood; so more of a basic science study.

So the current status of this repository is that there is a phase one repository of approximately 5,000 unlinked samples. And secondarily, we've access to donor tubes on about 13,000 samples so they've been aliquoted into four subaliquots, and I'll get back to this in a minute.

Now the TRIPS study, which I'm not involved in, as I said, began in the early-2000's and it is still ongoing. Its main purpose is to use NAT as a adjunct to standard serologic assays to enhance the detection of known suspected transfusion transmitted agents to be able to look for DNA or RNA to -- so as to distinguish ongoing infection from just exposure, and allow for the observation of age-related differences, because about half the enrollees in this study are children, and the other half adults. It's also a resource for emerging agents, and it's also being used to look at immunological studies specifically microchimerism in transfused patients.

It's got some different characteristics; it's been done only in a single metropolitan area here,
basically the NIH Clinical Center, and other D.C. area hospitals and blood centers. It is a linked donor-recipient repository. And the aim here was to try to put away all donor specimens to a given recipient. This has been accomplished in a majority of cases, but again, because of competing blood supplies not all cases. All of these units are leukoreduced, and most are irradiated.

These investigators decided to enroll heavily transfused patients, regardless of the degree of immunosuppression because they're doing NAT assays they don't depend on antibody development, so there are a lot of stem cell transplant patients, and the like, in this repository. Again, they have the better recipient sampling strategy of frequent post transfusion samples, at 4, 8, 12, and 24 weeks. And they have also frozen whole blood, as well as plasma and serum.

So, in summary now, what can we say about these repositories, they've been used for many important studies in the field of transfusion transmitted infection, including evaluation of agents that were not known or deemed important at the time the repository was established. Donor-only repositories can be used to
Recipient-only repositories can give us clues to transfusion-transmission because we have a pre-transfusion sample that's negative and a post-transfusion sample that's positive. However, we can't prove that it was the donations that caused the infection; nevertheless, we get useful data. But it's the linked repositories, donor-recipient repositories that can serve -- that can do all of these things. They've been used for many years. The types of studies have varied, but despite their usefulness, testing of repository samples will not always be able to answer new questions about transfusion-transmission. So you can see here that over time, some of the observations from these studies TTVS, TSS, FACTS have been useful to be able to chart the prevalence of infections over a 25-year period.

Now, in the last couple of minutes I want to talk about the current status of these repositories because many of these are under the control of NHLBI, which funded these studies. They have custodianship and they've established what they now call the NHLBI Biological Specimen Repository which acquires stores and
can distribute these samples. It's actually been in place for 35 years, but it's really taken a new form in the last few years, it includes over 4.6 million biospecimens from over 70 collections, so not just transfusion studies but all NHLBI studies.

The samples themselves are probably just up the street because they're managed by SeraCare, in Gaithersburg. And as you can see, there -- of 73 study collections, but by far the most of these samples are from blood banking and transfusion medicine, with fewer from heart and lung disease studies.

And in that you can see these -- the largest sample sets, and these are numbers of tubes are from these REDS donation repositories, and then you can read around the wheel here, the RADAR study, the TRIPS study, TTVS with 250,000, et cetera. And the ones here -- this is just a redo of the previous slide but the repositories in the pink here are ones that are under control of the NHLBI biospecimen group, the other two in white are still under control of the primary investigators.

So the news here is that if the NHLBI controls them scientific -- and there beyond the -- beyond the
study period, these are accessible to anybody in the scientific community through a specific application process with a good study hypothesis and funding to study these. And this is now managed through this new network, called the Biolincc network, which manages both the NHLBI clinical study data sets that have been transferred, and the repositories. You can access these guys on the web though, the website is down here. And you can actually see how you might go about applying to test some of these samples.

But it really depends upon whether the clinical study is ongoing or just concluded. That's the proprietary period which usually lasts for two to three years after completion of the study, and then when that's over, then it's in the open period, as I'll show you in a minute. But the investigator wanting to study these samples must have funding and then they can get access through subaliquots.

And the proprietary period is defined as follows, the study collection is complete, but the parent study is still ongoing. So for example, the TRIPS study still controls all of their own samples, but the open
period is when the study is complete, and the review processes -- you have to submit a request and it's reviewed by an external committee that decides whether it has enough merit to go into these important repositories.

So my last slide is to sort of bring this all back and say we have these resources. We'll be talking about XMRV later today. Are any of these resources a good resource for XMRV studies? And I don't know the answer to that; maybe we can discuss it later.

And then, if we are going to use it -- these repositories, what criteria should be fulfilled prior to accessing them? Well, I think, clearly, we want to have good assays, and we want to know that the prevalence in the donor population is -- we want to have some clue that there's some prevalence. But how high would be necessary before you do it, a linked donor-recipient transmission study. And just to say currently, PHS is -- or HHS is doing some panel studies of newly collected samples to try to validate assays. And when that work is completed, perhaps this -- these will be good samples resources.

So I think I'm getting you closer to your coffee, and I'll close there.
MR. NAKHASI: We may have one or two questions for Dr. Steve Kleinman.

MR. KUMAR: Hi, Sanjay Kumar (phonetic), from FDA. A very nice and useful presentation, Dr. Kleinman, excellent. What are the future plans? Any -- are any prospective studies, plan for specimen collection?

DR. KLEINMAN: So the question was, are there plans for future repositories? I think NHLBI, who funds most of this work, would be the people to answer the question. But I think the last time this was sort of examined a few years ago; the thoughts were these are really incredibly expensive resources to put away. And the administrative steps to do it, I mean, the planning is a year or two before you can even collect samples.

So, other than the ongoing TRIPS study which is still putting away samples, I'm not aware of attempts to put away future large-scale repositories like this. Again, it may be possible to put away some donor samples,
and blood collecting organizations often put away samples from donors. But collecting linked donor-recipient samples are difficult. One thing I didn't mention is there are also samples that I believe are under more primary control of the network that CDC runs from both hemophiliac patients and patients with chronic transfusions like sickle cell and thalassemic patients.

Now, hemophiliacs don't get diseases anymore from plasma fractions, so they are no longer a good sentinel population, but it may be that some of the chronically transfused patient samples can be accessed, but again, they're not linked to donor samples. So I think the summary -- a statement is these are the repositories we have, I don't think we're likely to get any in the -- any more in the near-future.

MR. NAKHASI: But I think I want to follow-up on that. I think the theme of this -- today's workshop is really to see how should we be prepared for emerging infectious diseases? And in that context, I would want to have a discussion; maybe at the panel later on, how should we engage ourselves in developing such repositories. And you mentioned the TRIPS is a -- only a local repository.
It may not represent the epidemic, for example, anywhere else going on. So I think those are the questions we should keep in mind, and have a discussion at the panel session.

DR. KLEINMAN: Yes, thanks Hira, because there is -- the question was, were there any plans up till now? And I don't think so. But of course, these can be revisited and new plans can be generated.

MR. NAKHASI: Mike?

MR. RUSH. Hi, Mike Rush (phonetic). Yeah, I think what you highlighted, these very large repositories one, are very expensive, and logistically difficult to build, and temporarily and geographically focused. And I think the future, and what we're seeing some examples of, are more rapid response repository capacity. So for example, Philip Norris and Su Stramer have begun to collect post-donation specimen. So donors call back with illness and those samples are tapped in to quickly, the donation materials that are being used, for example, to look for influenza and virus discovery.

For XMRV, we were able to quickly begin to collect specimens from the Reno-Tahoe donation area, which
was the area where there were focal epidemics. So the idea, and with West Nile -- the idea that you can turn on acquisition of samples from donations essentially in real-time because these samples are flowing through these large centralized testing labs, and you can tap into plasma or whole blood.

The donors typically now, you know, are being consented in a way that enables some level of research study with appropriate subsequent IRB approval. So I think in the discussion, rather than -- I do think these huge linked donor-recipient repositories are valuable and should be built at, you know, some frequency, but they have limitations.

And so many of the kind of things we're responding to now are so focal and temporal that we really need to be able to have systems that can pull the trigger to save the samples from the donations. And unfortunately, we don't have pre-transfusion samples from recipients but these are usually transfused products, so as necessary, look-back studies could be undertaken to look at transmission.

MR. NAKHASI: All right, I think with that we'll
break for coffee. And I think we should be back in the next 3 minutes, I guess, according to this.

(Laughter)

BABESIA VS XMRV, WHICH WAY?

DR. KUEHNERT: -- pleasure of introducing him. He was born in England some time ago. And has been at the American Red Cross for 39 years, he's the current vice president of research and development, and director of the Holland Laboratory, and is responsible for the Red Cross research programs supporting its blood program.

He's authored more than 175 publications, and has edited three books on transfusion transmitted infections, and has been an advisor to WHO, served on the editorial boards of Transfusion and Transfusion Medicine Reviews, and is a past president of AABB. His awards also include a John Snow Award from the American Public Health Association, and I can personally attach that he's been an essential collaborator on public health issues related to blood safety.

He's going to be speaking on the EID issues with
the provocative title "BABESIA VERSUS XMRV; WHICH WAY?"

Dr. DODD.

MR. DODD: Well thank you very much Matt for that very kind introduction. Yes, I suppose I could start talking about the road less traveled, but in fact I was asked to give case studies on Babesia and XMRV, as being illustrative of really two agents that are in our eyes at the moment. And really at very different stages of the decision process; and perhaps they'll be a springboard for better informed discussion as we move thorough the rest of the day.

So what I want to try and do is to talk a little bit but in generalities about available information for each agent. The current environment in which we sit, some discussion about prioritization, and here I've already pre-stolen a lot of Susan's slides. And Susan, please accept my thanks and apologies for doing that.

Talk a little bit about some of the options. And go back to some conclusions about whether we go down one path or another or if we try to do some quantum split here. So I think that this has been discussed already all through the morning, what critical information that we
need about EIDs to assist in thinking about decisions.

And Jay very nicely covered these through an asymptomatic blood-borne phase through an agent, has transfusion-transmission been observed, and this is, I think, fairly critical. Does the agent survive component manufacture and storage? Does the agent cause disease, and again, this is an important aspect of the discussions we need to have. If there is disease, what's its severity, mortality, and is it treatable?

What's the donor prevalence? And if you have interventions in place what's the incidence? Is the agent changing in its epidemiology? And Jim Hughes talked a great deal about this, but we haven't focused on it very extensively in the blood context to date. And a very important aspect is what is the professional, regulatory, and public concern. And as you'll see, this may sit on a very different axis from the public health aspects associated with infection. Are there interventions that were available and would their implementation have a rational impact on the resources or a survivable impact on resources?

So let me just talk a little bit about each of
the agents in this context. So Babesia is an intraerythrocytic, tick-borne, protozoan parasite. It can cause asymptomatic infection, which may be prolonged. And David Leiby's group have shown some very extensive asymptomatic infections in the donor population. We're certainly aware of more than 70 transfusion transmitted disease cases for this agent. And Barbara Herwalt (phonetic) is reviewing these, and has hinted that the final answer, at least in her estimation, may lie between 100 and 200.

The agent does survive in red cells and in platelets albeit probably in red cells contaminating platelets. And the disease caused both naturally, and in transfusion recipients ranges from asymptomatic to fatal. It is nominally at least treatable, but if it isn't picked up early enough, and if the recipient is particularly susceptible, this isn't always the case. In selected areas in this country the donor prevalence of seroprevalence may range between 1 and 2 percent. And in fact look-back studies have shown infection rates of perhaps 1 in 1000. But in a very localized sense, again, as Jay pointed out.
This is a somewhat expanding or emerging infection, and has been a significant regulatory and professional concern about transmission of T. cruzi by transfusion. At the moment there's no licensed tests, there are some testing services or some tests available commercially. And recently there's been an SBIR proposal to stimulate interest in the development of tests suitable for blood screening.

And the regional -- original program of testing is conceivable. And I believe that the outcome of implementing such a program would be reasonably predictable based on the information that we have so far. And these are some data largely collected by Annetta (phonetic) and others in the Red Cross program that I present just to show the increasing frequency of reporting of post-transfusion Babesiosis in our population of donors and recipients.

So the current status, in my view, is that we have a large knowledge base with reliable information on the disease, its treatment, its epidemiology, its infectivity, and potential interventions. We know that there have been and will continue to be a significant
number of transfusion transmitted cases. There is a donor criterion in place, and it's been in place for many years. Although the evidence is that it has no demonstrable value in ameliorating Babesia transmission by transfusion.

An IFA testing system is available, and consideration has been given and will continue to be given to selective testing, that is testing only in regions of concern. Of course, there are complications in the transfusion arena, such as the transport of blood around the country that may impact this concept. And in terms of just one source of public concern, we talked -- in fact, Susan talked to the Red Cross PR people, and we've had once query about Babesiosis in the past 3 years; not a hot button issue.

I think the scenario for the future for the agent itself in the U.S. will be a slow geographic expansion. There is a current effort on -- and this is largely due to an increased exurban lifestyle, bringing us as Jim pointed out, into closer contact with animals and animal environments. There is a potential for a national reporting requirement which inevitably will push up the number of noticed cases. We are getting increased
attention. There was an FDA workshop not too long ago. And I think there's a predictable moderate growth in transfusion cases.

And an important point, which we'll come to in the context of the other agent, is the likelihood of significant change in the pathogenicity of this agent is unknown, but in my opinion is likely to be very low.

Now, Lou Katz (phonetic) said "Gosh, if you remember this you must be old." And Matt's already hinted about this, but there was an interesting movie, and it brings me to the topic of XMRV. Everybody's lips, Xenotropic Murine Leukemia virus-Related Virus. It is a Xenotropic retrovirus, that is one that can no longer actively infect its host organism, the mouse, or apparently the mouse, but can infect other species. It's a cell associated virus with an unknown transmission rate to and between humans, and appears from genetic data to be of Murine origin.

It certainly generates asymptomatic infection, and to date we have not observed or indeed even looked for transmission by transfusion. The assumption is that a virus of this nature should be transfusion transmissible,
but we have no data to support this. There's no --
equally, there's no information about its survival in
blood products. We would assume that it would survive,
but we don't know. And to date we don't have any known
causative relationship to disease. And I think that this
is an important point.

There are data that suggests the virus is
responsive to the usual range of antivirals, and the
prevalence of infection in the donor population is
unknown, or have been scattered observations suggesting
somewhere between zero and three or four percent,
depending on populations looked at, tests used, and there
may be more data coming down the pike in the nearly --
ne future.

The epidemiology of this agent is unknown, but
there's considerable media interest, and there's a great
deal of interest from a patient affinity group, this is
the Chronic Fatigue Syndrome patient group, and there's
general regulatory concern about retroviruses, and
specifically about this agent. Any intervention that we
could conceive of at the moment assuming that the decision
was made to develop an intervention would be strictly at
the research level would be of unknown value and questionable impact, both in terms of its efficacy in preventing a future downturn or downside, or of its impact on the availability of blood and donors.

The current status is that there's highly controversial literature, there have been inconsistent findings for viral markers of infection with XMRV in various prostate cancer populations, and in patients with chronic fatigue syndrome, and healthy controls. But no causality has been established in these cases.

And there are publications that define such a presence; there are many counter-publications that fail to find these associations. So I think at the moment the jury has to be out on what the significance is of infection with this agent.

As I already commented, transfusion transmission is theoretical; we don't see an obvious intervention to prevent such transmission. And test methods, as Steve already pointed out, are not yet standardized. Now, there's certainly very general concern when HIV is seen as the model of an evil retrovirus, with particular focus on two aspects, species jump, and potential for mutation to
become a pathogen.

But we have to note that to date, in the published studies, this agent has had a very stable genomic structure, which suggests that it's not out there mutating furiously. As I already commented, the CFS affinity groups and their surrogates are very interested in this agent. And just yesterday, the CFS advisory committee came up with a recommendation to screen blood donors for CFS by a questioning focus. We'll have to see where that goes.

And Canadian Blood Services, the Australian Red Cross, and the New Zealand blood system have already instituted or confirmed a permanent deferral for individuals with a medical diagnosis of CFS. The Red Cross has had seven -- at least seven recent enquiries, here's one of them. And this is fairly typical of the sort of general tenor of what's going on.

I won't read it, but it comments on the Canadian decision, the Red Cross -- since this was the Red Cross needs to be on top of this, so people in the U.S. are not getting infected by people with CFS, please ban people with CFS from giving blood, as the Canadian government did
last week. It wasn't actually the Canadian government; it was the Canadian blood services.

There's a lot of information that we really need to be in a position to think seriously about this agent. What is the gold standard test that could be used diagnostically or indeed as an intervention? What is the prevalence, incidence, and what are the risk factors for this agent in the donor population. Are these rates changing? And what is the transmissibility by transfusion, and if so, what is the impact of transfusion transmitted infection, particularly with respect to disease causation. And there is indeed again, as Steve pointed out, an HHS workgroup that's trying to deal with these issues in a systematic fashion.

What are the scenarios for the future with respect to XMRV? I would submit that at this time they're completely unknown and essentially unpredictable. And again, in my opinion, range from the completely irrelevant, to a doomsday scenario. The irrelevant situation is that this is a phenomenon reflecting contamination, cross-reactivity, or even normal viral flora.
And in the latter case, there is certainly some models where we have viruses that are widespread, that are transfusion transmissible but which do not appear to cause any negative outcomes either to donors or recipients. The TTV/SEN-V complex, HGV/GBV-C, and even simian foamy virus have all been discussed in this context. And we appear to be relatively comfortable at this time, paying no further attention to them.

The doomsday scenario of course is the one that provokes a lot of concern that the virus causes a dread disease or diseases. That it has an extended incubation period, that it spreads rapidly by common routes, that it's already widespread. And perhaps there has been or there will be a viral mutation event. This is -- this I think is something that has to concern us.

So the balance is, on the one hand, we have an -- a disease or an infection with a long-standing information and a predictable outcome, and a new or newly recognized agent with unpredictable outcomes; where do you go from here? I spent a little time considering whether there are any precedents from things that we've done since the appearance of AIDS. And I find really not a lot; HTLV
we took rapid action because after all, it was a retrovirus.

HCV, yes, but this was a high prevalence long-known agent that was well-known as associated with a disease we'd been trying to grapple with, as a transfusion transmitted outcome for many, many years. vCJD, another dread disease with a vanishing but known incidence and prevalence, not present in the U.S., no known transfusion transmissions one time, no tests, but nevertheless a massive donor deferral program. And -- and so it goes, West Nile Virus we acted rapidly and effectively, T. cruzi a little bit more like Babesia, if you like, lots of information, lots of research. And increasing focus on an intervention. When the intervention came we started to decide that maybe we didn't really need it.

Simian foamy virus, actually gone to BPAC, the Canadians defer monkey handlers, and we have done nothing about it. I don't think that the past gives us useful precedents, which I think is another reason that we're having this workshop. But this leaves us really not knowing which way to go in my opinion.

So the question that we really need to focus on
perhaps is how do we prioritize in these circumstances? And as Susan will discuss in much more detail, I think we have to be concerned that there are really two axis that don't interact very well; the axis of public health which is the benefit of an intervention, and the access of public concern, which is basically panic.

And underlying all of this is a decision-maker's dilemma; how will a decision on this topic be judged in the future? So we'll hear much more about this later, but there has been a pretty significant effort put on by the AABB's TTD group, and ably and effectively led by Susan to try and come up with a listing of transfusion transmissible agents or potentially transmissible agents. And to develop some sort of a mechanism for prioritizing them.

And the top priorities were actually put on this matrix that compares science and epidemiology with public perception, and actually the outcome of this puts Babesia in a fairly high priority arena. XMRV, I honestly don't know where one might put this. And after I put this slide together, I thought, well maybe this isn't even the right shape, maybe we need something that's much more irregular
and doesn't have a clear position anywhere on this matrix because my sense at the moment is probably the public concern access is higher than the science and epidemiology. But we really don't know.

And just to put this in context, and you'll hear a little bit more about this, the AABB group really sorted out three priority levels plus a long watch list. And the RED priority are ones with a high epidemiological and scientific evidence of safety risk, along with a high public concern. And I'll just comment on YELLOW which is where the scientific evidence is low or absent but there is public or regulatory concern. And Babesia, by our lengthy discussions and no particularly rigorous set of criteria, although we worked very hard on it, is up in the RED axis. XMRV has been suggested should be in the YELLOW arena at the moment.

Now, one tool that's often touted in terms of making decisions around these issues is the precautionary principle, which actually in its original formulation was an environmental concept. And it said, don't take an action unless you can establish that it will do no harm. But in its current embodiment, we think of it as action to
prevent harm should be taken even if its value cannot be proven.

But this precautionary principle is often cited without thinking of some of the caveats that come with it. And the supporting commentary is very important. It says that all action should not be disproportionate, and we shouldn't aim for zero-risk. Comparable situations should not be treated differently. We should act in a way consistent with comparable situations in known circumstances. And costs and benefits might be considered where appropriate and feasible -- all risks and benefits.

And a decision should be provisional pending scientific information. And in one of the better commentaries on the precautionary principle of Vecchia and Repacholian Science, this comment is made, “Viewing the principle as part of a process for making provisional decisions about risk management under uncertainty would reduce criticism from its more fervent critics or advocates for more extreme interpretations of it.” In other words, it's not an absolute.

So what can we think about as options for Babesia? We could implement blood donor testing. Testing
services and tests are available in a limited fashion albeit not licensed, the methods are sub-optimal for our environment, the risk is variable regionally, and there may be manufacturer reluctance to produce adequate tests for a relatively small market.

Other interventions though really don't appear to be currently available. We could continue our research but to what end. I submit we know a lot about this agent. And doing nothing is an option, but it doesn't seem to me to be a very good one.

XMRV, on the other hand, we could continue research to establish information for appropriate decision-making. We could consider an interim blood safety intervention. Testing? Perhaps not, we don't have standardized tests. Again, the commercial markets uncertain, we don't have a disease association although it may exist. And we would have an unknown impact on the blood resource.

Deferrals, well, disease as we've already seen would be a very uncertain surrogate for infection and infectivity. And the risk factors for infection are not at all apparent at the moment. And education and self-
deferral might be a relatively harmless procedure, but who would be educate? And who would we self-defer? And again, doing nothing is there, pending accumulation of consistent data.

But do we really need to prioritize? Do we need to choose one path for another? And this is really my summary, the current and future blood safety risk associated with Babesia is well characterized and broadly predictable, and there's enough information to make a reasoned decision.

But at this time there is no way of establishing the quantitative or qualitative risks of XMRV to blood safety, and there are no available meaningful interventions. But responsible research would be expected to resolve some key uncertainties. And test implementation and research involve completely different resource pools.

So this is where I end up at the apparent split in the road; Babesia we should seriously consider donor testing, we're in the right position to make that decision. And XMRV, I believe is still subject to research although there are significant public policy and
public concern overheads here. Thank you very much.

(Applause)

Q & A

DR. KUEHNERT: Thank you Roger. Are there questions for Dr. Dodd?

MR. NAKHASI: Roger, don't leave -- oh, Peter has a question. Dr. Ganz.

DR. GANZ: Peter Ganz from Health Canada. Roger, I just wanted to comment, I guess my soapbox is simian foamy virus, and again, I think our thinking at least in the (inaudible) context was that yes, there is no pathophysiology attached to the virus, but having a retrovirus in the human population spread through transfusion is probably not a good idea, whether or not there is genetic drift or whether or not over time mutations will accumulate that could make it pathogenic is not something you want to gamble with.

So -- and again, looking at the other side which is impact on donor blood supply and so on, it's relatively minor, so that's the background comment.
MR. DODD: Wow, my comment is, Peter, unless you're even more unusual than I suspect, you're 8 percent retrovirus already so --

MR. KATZ: Louis Katz from a small blood center in the Midwest that's becoming larger. I just wanted to clarify something for the people in the workshop who are not paying attention to the XMRV interventions around the world. In all three cases that you cited, Canadian Blood Services, Australian Red Cross, and New Zealand, they're not querying their donors about a diagnosis of Chronic Fatigue Syndrome. They are excluding donors who volunteer that history in the absence of specific donor questions.

And I think that probably is, as discussions are carried forward during the workshop needs to be clearly understood.

MR. DODD: Thank you Lou.

MR. NAKHASI: So in that vein -- so Roger, what would you think we should be proceeding with regard to XMRV?

MR. DODD: Well, as I say, I think -- as I try to say, I think there are two different axis that we need to consider is, as scientists we need to consider what the
data are or are not telling us, and what responsibly could be done in the short timeframe to provide adequate information to really know what's going on or what might be going on.

From a public policy point of view, I think there's a lot of pressure, there's a lot of pressure particularly from people with CFS, which is a disease of considerable concern, and their belief is that if this is -- does have an infectious cause, and that's a very open question, shouldn't we be reducing the risk of transmitting this to other people. But the problem of transmission of XMRV if it is a problem, it's going to be very much bigger than I think CFS alone.

So I don't know what the answer is. I think those we'll probably discuss later. We do need a realistic system, but I don't know how you trade one against the other. But Jay is going to tell us what to do.

(Laughter)

**DR. EPSTEIN:** Not this minute.

**SPEAKER:** Roger, I kind of liked the way you summed up that it's not necessarily an either-or choice
when we talk about prioritization. From where I sit, we are really never relieved of the responsibility to look at all times at all risks. The question that we're really asking ourselves, which I think is summarized on this slide is, what's the appropriate action now? And I think the ultimate question is, do we intervene?

And so just -- what are your thoughts about just the word prioritize? Because again, I don't really see it as you know, we've put off the issue two because we're concerned with issue one. It's more what can we be doing now with issue one and issue two?

MR. DODD: I believe that the path is reasonably clear for issue one, which is that this is a disease that's going to continue to occur. That is Babesiosis. It's going to continue to occur in blood recipients and for which there are relatively presumably effective measures to manage. And I think that we can move ahead with this, and perhaps initiate some testing, some broader seroprevalence in a fashion that will do some good, that will teach us a little bit more.

In the context of XMRV, I think that there is an emergency, but it's a perceptual emergency. And I'm not
as well versed in the tools of managing that, but I think that what we need to do is to manage people's reactions rather than people's safety at this point. I hope during the day that somebody can come up with a mechanism to manage that.

DR. KUEHNERT: Last question.

SPEAKER: (Inaudible). Just a follow-up to the last comment that Roger made that I agree very much, and I think you touched the important point, is that I believe that we are going to confront this type of issues more and more frequently. It became a pattern with for instance, Gulf War syndrome, and all that where affinity groups as you called -- have adopted transfusion as a way of calling more resources to their issues.

And in fairness to them, it's a very serious problem and they haven't gotten enough in attention and support. But I think that we have to be able to deal with the issue because it is going to become more frequent than it is now.

MR. DODD: Thank you. I'm glad you said it, not me.

DR. KUEHNERT: Okay, thank you Dr. Dodd.
EMERGING INFECTIONOUS DISEASES AND RISK FOR TRANSFUSION SAFETY: AABB PRIORITIZATION PROCESS

MR. NAKHASI: The next speaker is Dr. Susan Stramer. She's going to be talking about the emerging infectious diseases and risks for transfusion safety prior to AABB prioritization process. A few words about Dr. Stramer. Dr. Stramer is currently in the -- at the American Red Cross. She's joined American Red Cross in 1995 as a laboratory director for National Confirmatory Testing Laboratory.

She's serving now as an executive scientific officer within the biomedical service medical office where she provides scientific leadership in the area of infectious disease for National Testing Laboratories, blood collections in regions of the Red Cross. With that introduction, Susan -- and brace yourself.

I think that Susan has not that many slides today. So I'm -- I have warned her to that -- not too many slides.

MS. STRAMER: Thank you. Can you -- I'm
projecting okay? Okay, yes, Hira's quite right. I have fewer slides than the last time I gave a related talk which were 98 slides given at the speed of light or perhaps at the speed, this volcano, if you can pronounce the name, was ejecting ash over Northern Europe. And the analogy here to the volcano is these are difficult -- natural disasters are difficult to predict.

They're emerging -- they're actually increasing in our planet. So maybe we can take a lesson from this, the uncontrollable and unpredictable nature. But anyway, what I'm going to talk about is the AABB prioritization process for emerging infectious disease agents and the risks for transfusion safety. So where are we now in 2010.

Modern technologies have reduced the risk of classic transfusion transmitted infectious agents to very low levels. New infections continue to appear and the old ones continue to spread. The horizons of blood safety have therefore expanded rather than contracted. So I guess one can look at this as job security.

Roger and Jim Hughes have already referenced the product of our AABB work group, which is a subgroup of the
Transfusion Transmitted Diseases Committee which was a transfusion supplement they'd published in August 2009. It's also available on the web and the web address is here in yellow. And we -- I selected for the cover, different agents that were prioritized as part of our process and some of the vectors, without much thought, Q fever which has already been mentioned several times.

We've a little picture of Coxiella burnetii, just a random -- I like the agent, so it would up on the cover. The article was put together by myself and I already referenced the subgroup of individuals from TTD. The primary individuals are listed on the title page of the article.

And I'd like to acknowledge many of which are here, Blaine Hollinger, Lou Katz, Steve Kleinman, Peyton -- I haven't seen; I don't think he's here -- Kay Gregory who after this assignment, has fully retired and Roger Dodd. And if you read just a few sentences in the background, you can get a sense of what we do. Emerging infections have been identified as a continuing threat to human health.

Many such infections are known to be
transmissible by blood transfusion, while others have properties indicating this potential. There has been no comprehensive review of such infectious agents and their threat to transfusion recipients' safety to-date. So we try to fill that void. There are many contributors. This was a very complex project.

They come from many areas, private and public sector. Many are sitting in this room and you can read who they are and where they come from on this list. And we acknowledge and thank all of them for their ongoing participation. One thing I should mention is this project hasn't stopped. The supplement, I guess, is only the beginning.

We continue to meet and we continue to argue about agents, how they should be prioritized, and on what we should communicate about each agent. So we started this over 4 years ago and what our goal or charge to TTD was, was to list and describe known and potential EID agents including -- bioterrorist -- bioterrorism agents, which I want to talk about in great detail for which one, the transfusion or transplant transmission is documented or its potential exists.
That is they have a known blood, organ or tissue phase. And two, no effective intervention exists. We focused on the United States and Canada. So when we talk about intervention, we consider agents even if we were doing health history questionnaires or travel questioning such as for variant CJD. We still included those agents because the questions really refer to risks outside of the United States.

So if we have, for example, a vCJD epidemic in the U.S. or a malaria or tetanus outbreak in the U.S., the questions that we ask today really wouldn't be very effective. The agents that we considered are put into various classes in order of increasing nucleic acid with prions having none, viruses, rickettsia, bacteria, protozoa, and we had one nematode.

This exercise started with a two by two table, just putting agents on a y-axis and characteristics on an x-axis. And we rapidly realized that wasn't going to be very effective to fulfill the charge we have. So instead we created fact sheets and the fact sheets are all posted on the web. They describe the agent, its relevant characteristics, risk to recipient safety, possible
interventions.

I won't go on, but there are 28 attributes. We also not only created the fact sheets to describe the agents but we've already discussed priorities. And we did prioritize agents as to their blood safety threat. We wanted to send a message to industry and that's all of us in this room, regarding preparedness.

We need to continue with research including surveillance, infectivity models or infectivity in recipients as we have bio-vigilance, testing methods and pathogen reduction technologies -- it shouldn't be either/or -- we likely will need both as we move forward -- and policy development. So we've already defined an infectious disease agent.

Here I listed again from the Institute of Medicine, "Those whose incidence in humans has increased within the past 2 decades or threatens to increase in the near future. Emergence maybe due to the spread of a new agent, the recognition of an infection that has been present in the population, but undetected or to the realization that an established disease has an infectious origin. Emergence may also be used to describe the
reappearance or reemergence of a known infection after a decline in incidence."

So why do we have infectious disease risk? Emerging agents is really only one reason and those with an absence of interventions. We, even with the testing that we do or the donor selection or screening that we do, we may have a failure. We may have tests that do not detect prevalent donors.

We can have earlier infections or those that are not detected by our tests. That is window-period infections, tests that we use or the agents for which testing we do, may have -- may mutate or we can have variant organisms or we can have a frank laboratory failure. Of course that never occurs. So what are the requirements? This has also been touched on by Jay, Roger in their talks.

We need to have an asymptomatic blood borne phase otherwise donors wouldn't present. This can -- this relates to both chronic and/or acute infections. The agent must survive in donated blood. There's already been a reference to T. cruzi or Chagas disease and probably this is the control point here why we haven't seen more
transfusion-transmission for T. cruzi.

The agent is very fragile and probably doesn't survive the way we process blood today versus the earlier literature when whole blood, very fresh whole blood was used and associated with high rates of transmission. We need to have an agent that's infectious by the IV route. We need susceptible population, recognize disease in recipients.

And the level of concern is dependent on the severity of disease in the recipients, incidence or prevalence in the donor population and the rate of emergence of the specific agent. So why do infections emerge? There's no single answer and all of these have some level of interplay. We can have a brand new agent as we did for variant CJD.

Species jump as we've already mentioned for HIV, SARS and perhaps -- or we don't know, XMRV. We have environmental changes such as global warming that can influence and does influence the spread of dengue virus, Plasmodium and Babesia. These agents are all expanding in their range.

Failure of control measures due to drug or
vaccine resistance, HBV mutations that may not be detected by the tests we do which -- and we don't think of HBV as emergent infectious agent, Plasmodium. Population movements such as T. cruzi or chikungunya virus, which we all know has spread to many areas of the world. Transportation of agents, reservoirs, other vectors such as West Nile or monkeypox virus and a giant pouched Gambian rat.

Why anyone would want to have one of those as a pet is a mystery. Behavioral changes, acts of conflict, changes in dietary habits or sanitation, hepatitis E, Leishmania or HIV. Interaction -- inactivation resistant agents, we'll probably -- and we will talk about pathogen reduction, but not all agents will be sensitive to the reduction or inactivation agents we use such as B19, HAV or prions.

We need to have susceptible hosts and lastly, we create some of our own misery in the way, for example, we do intensive modern farming practices which has led to vCJD and now to Coxiella burnetii or Q fever outbreaks. So how did we prioritize? We identified 68 agents, 69 now if you include XMRV. It includes all classes of agents,
all without an existing effective intervention.

    Most has already been referenced -- are vector borne or zoonotic infections. They involve many transmission routes. They can result in acute or chronic infections. Many derive from human activities. Transportation has a critical role. Emergence, as I mentioned, is unpredictable and the bottom line is that there are no features common to all.

    So how do we prioritize? Roger has already alluded to the two axis we used and that came from an article in science from Slovic, where they -- he described -- an unknown risk versus a dread risk on two separate axis. And the public is more willing to accept an unknown risk, which has a delayed ability to cause harm.

    And that's basically the scientific axis versus a dread risk, which has lack of control or is viewed by the public as catastrophic. So we translated those to a science/epidemiology axis versus a public perception axis. And the public perception axis, in its most extreme form I guess, is what Roger discussed.

    We know Babesia is expanding. It's unequivocally transfusion-transmitted, causes fatal
disease in recipients and the Red Cross has only had one query in 3 years versus over the last 6 months, we've had over seven queries now for XMRV in which transfusion-transmission hasn't been proven, clinical disease association haven't been unequivocally demonstrated.

So it's really -- public perception is quite a tricky axis to deal with. So who is the public? We included the regulators, that is the FDA or we should have -- I should have also put Health Canada since we considered the U.S. and Canada.

Had we got public information we can get it through the blood products advisory committee, the advisory committee for blood safety and availability that is open public fora where the public has an opportunity to speak. We get blood center inquiries which I've already referenced. The AABB gets inquiries.

We have media coverage. Certainly the Wall Street Journal is becoming one of the leading medical journals. And perhaps public concern is disproportionate when it comes to blood safety. The public feels we have control of what we issue in blood products and we have a history with HIV to contend with. I don't think anyone in
the U.K. if you flash a cow on the T.V. set, the first thought in their mind is probably BSE. So we've done a really good job with educating the public.

Roger touched on how we prioritized RED being the most severe or low to high scientific epidemiological evidence of blood safety combined with heightened public or regulatory concern. ORANGE is kind of in between. We've prioritized the agent but it yet doesn't reach the RED level.

And YELLOW is really a regulator or a public perception category, where we don't have enough science or epidemiological data to really give this a very high priority. But we know the concern is there. So these agents have already been referenced, dengue, Babesia, vCJD, all zoonotic, two of three are vector-borne agents.

ORANGE includes the agents of malaria, Chagas disease, Leishmania, St. Louis encephalitis and chick virus. YELLOW includes the last prion chronic wasting disease. I shouldn't say the last -- we didn't prioritize Creutzfeldt-Jakob. We only prioritized the variant. HHV-8 variants of HIV, Borrelia, influenza whether you call it H5N1 or 2009 AH1N1, Simian foamy, Parvo and HAV.
So this may not apply to all situations. This is the way one group of experts put the priorities together. We didn't at that time prioritize XMRV, but I do think it fits under the category of YELLOW and we didn't prioritize at that time, Q fever, and maybe we would have managed Q fever differently now if we did then. So this is our x-y plot and the corner in -- it's the top corner here reflects worst case outcome for both public perception and science and epidemiology.

It was difficult to pinpoint one specific place for each agent. So even though we gave categories of absence to high for public perception or theoretical to high for science or epidemiology, often there was a range.

So for hepatitis A, for example, we believe it has -- may have low scientific reason to introduce an intervention. But public perception depending on where you are or what you know may range from being absent to perhaps a moderate concern. We also consider pathogen reduction.

We provided a lot of information on pathogen reduction because we didn't want to just say an intervention is a testing intervention. It can be as Jay
said the Holy Grail and be a process to reduce all pathogens or potentially to reduce all pathogens. They are limitations. We have long regulatory cycles to prove safety and efficacy.

The risk potential toxicity perhaps we haven't monitored recipients who've received blood components treated with these agents long enough to know if there is toxicity or long-term toxicity and there may be agent resistance, as I've already mentioned. So our challenges are that infectious agents will continue to emerge. We can target zero risk or evidence based that we often discuss but the public drives a lot of what we do.

Unfortunately, there's a lack of interest participation now from our manufacturers due to shrinking markets and shrinking margins. Regulatory demands and cycle times are long. So the question is where will funding come from as these threats continue to emerge. And our current technology becomes antiquated. I just want to go through why we selected some of the agents we did as RED agents.

So what do these agents have in common? They're known transfusion-transmitted. They've an increasing
worldwide frequency or perhaps their frequency is unknown. They produce clinically apparent or fatal disease in recipients, may not be properly diagnosed if a recipient is infected and most without specific treatment -- I said most because there are treatments for Babesia -- all without an effective intervention.

And I've already told you what those agents were and we've already asked this question where does XMRV fit? Roger showed the slide for Babesia. Babesia is on the rise. Roger also mentioned that Barbara Herwaldt says there are 100-200 cases retrospectively in the United States and that doesn't occur what will happen today and tomorrow.

Dengue, also on the rise. Over 100 countries on this planet reports dengue infection. Dengue is hyper endemic meaning all four serotypes circulate on the island of Puerto Rico. I just showed the slide because as already mentioned, we have started an IND for dengue testing. We've already found three positive donors of over 11,000 tested, but what will happen this year?

The blue and purple lines show the historic range of what happens to dengue during the second half of
the year in Puerto Rico during the rainy season when there are outbreaks. In 1998, the first year in Puerto Rico where all four serotypes circulated, there was a huge outbreak.

And what concerns us for this year, which is in red, is that we've already seen a bump in dengue on the island and it's similar to that seen in 1998, which is highly unusual and relates to the very wet season that they've had on the island. So we don't know what will happen this year, but we are doing an investigational study to be able to get one test at least licensed, an antigen test.

CJD, perhaps the epidemic is waning. The black bar show you the epidemic in the U.K. The red bar show you that in France, 217 cases reported -- confirmed cases reported on ProMED. According to studies done in the U.K., they estimate perhaps there are 70 more cases of variant CJD waiting to be uncovered and for every one case that's clinically confirmed, perhaps there are 4,000 others that are sub-clinical.

These are the listing of cases. You can get this off ProMed. This slide I've gotten from the vCJD
surveillance unit via Chris Sprouce (phonetic) in the U.K. and Scotland, and it shows you of 66 recipients followed from a look back study of 18 donors who developed variant CJD that fears of transfusion transmission were realized. The four, top of the four bars, the x-axis showing you time since transfusion for the recipients to develop infection, in some cases greater than 6 years.

So these are the four recipients who did develop variant CJD, two from one donor and knowing that there is one recipient yet from that donor who has not yet been diagnosed or has not yet come down with infection. So for variant CJD unlike other agents for which we can do testing or pathogen reduction, probably an intervention for variant CJD will relate more to a prion filter.

So studies have been done showing leukoreduction can reduce prion levels from 42 to 72 percent but in these spiking studies for which efficacy of these reductions are very difficult to show. By the time we got to the prion filter, there was only one log to remove. But one log reduction could occur with the prion filters. And we've already made reference to XMRV. We have created a fact sheet just to touch on what we're doing for XMRV. We do
not have a donor specific question.

There is not one in use. We don't believe one is feasible because we cannot identify risk factors with any certainty. There are only experimental tests that have not been validated. It's difficult or impossible to ask a sensitive or specific question for CFS. If the studies have already been published of up to four percent donors is the reality, we would be losing many, many donors.

The specificity of XMRV infection in that four percent is unknown, and if we ask a CFS question, the sensitivity of that is also unknown if we're basing this on medically confirmed chronic fatigue syndrome because over 85 percent of CFS cases are unconfirmed and undiagnosed. And then lastly, do we do -- we haven't done anything yet for a donor deferral period that may change.

But this is currently what's in the fact sheet, that there is no FDA guidance or AABB standard. Current practice for FDA guidance and AABB standards is to accept donors who are healthy at the time of donation. Both CFS advocacy groups and the NCI have historically discouraged blood donation by CFS patients not only for their own
health but also to protect the safety of recipients since
the number of etiologic agents have been linked to CFS but
none proven.

And then last thing we said blood collection
facilities should follow their SOPs with respect to
cancer, that is the link with prostate cancer. So I leave
you with two slides to ponder. We have human RNA tumor
viruses or called "rumor viruses" and in the introduction
of this paper and Roger has already made reference to
this.

In humans, estimates from the genome sequencing
project suggest that indigenous retroviruses now comprise
some eight percent of our DNA. So we are walking
retrovirus factories representing around 4,000 pro-viruses
and 1,000 more solitary long terminal repeats.

And if you look at that paper just to show you
the number of retroviruses many or all of these for which
except for HTLV -- no HTLV is not on this table -- but we
do not test this list this long -- and has been associated
with cancer, neurological diseases, and autoimmune
diseases. So with that, I thank you for your attention.

(Applause)
MR. NAKHASI: Open for questions. Okay.

SPEAKER: Susan, I wondered -- you know, you had a discussion of prioritization and sort of how things come to attention and that was something was discussed earlier in terms of horizon scanning. And I was wondering what Red Cross or AABB does in terms of horizon scanning to determine, you know, that there is an issue besides, you know, press enquiries have come in or public inquiries or questions from FDA or CDC?

MS. STRAMER: We do the same thing basically as you all do. We scan the literature. We scan web-based services such as ProMED. So whatever is available, we put -- you know, we circulate among the core group. We've conference calls to discuss that, discuss which fact sheets need to be updated or fact sheets need to be added.

So it's a constant evolution of discussion and it's probably what we'll discuss this afternoon, how we use the tools that are available to us and communicate. And prioritization doesn't exclude one from another.
However, in the reality of operations or the reality of the way we function, certainly we can't do all. So sometimes, prioritization has to occur.

SPEAKER: I see.

SPEAKER: Hi Mike.

SPEAKER: Yet a couple of points on the last bit around sort of HERVs indigenous retroviruses. There was a paper last year that showed an association between expression of the HERV-K class of these indigenous retroviruses and lymphoid and breast cancer. And we got involved in trying to corroborate that with the collaborators.

And what we found is that actually the rates in healthy donors are of circulating plasma viremia are comparable to those that they are reporting in cancer patients partly as an affect of storage, delayed processing actually increases the levels. But the point is that we are -- we actually not only have these in our genomes but there is ten to the fourth to ten to the fifth copies per ml circulating indigenous retroviral derived particles in us.

And likewise, this whole family of TTV
(inaudible) viruses, we're all infected with them as very young children and we have substantial circulating levels of those viruses in all of us. So point is we now sort of appreciate that we have a viral flora in our blood just as we have a bacterial flora in our intestines and trying to chase these commensal agents in terms of their clinical significances is going to be a challenge.

But we just have to, you know, recognize that there are us. The question I have though was something like dengue arbovirus widely prevalent, spread extensively in these endemic countries through natural vector transmission, and you know, how do you balance in the level of endemicity of these agents when you begin to assess the transfusion implications?

And I guess how do you factor -- I mean if an agent is widely disseminated through vector transmissions to everybody and doesn't cause any more serious consequences from transfusion transmission, at least to our evidence, then while transmission, does that factor into the determination as to its prioritization, these will be transfusion intervention?

MS. STRAMER: Well, I mean we can ask that
question about West Nile virus. I mean disease outcome you know, from the disease that we had without transfusion has caused thousands of fatalities. And although the transfusion outcome, because the viral load infused from the unit of blood or FFP maybe much, much higher, we have that on -- we have that issue to grapple with.

And because we have the means and resources to introduce an intervention, even though the amount of West Nile that we're preventing by -- by screening is very, very small relative to the background rate of West Nile, we still do it. So I think the answer will really boil down to resources.

And countries that can afford to do blood screening, that's where those measures will be implemented. I mean in India, I don't see it be -- it's realistic for them to introduce a chikungunya virus screen or a dengue virus screen. But in the islands off East Africa managed by French blood services that have the resources to introduce these interventions, they do.

DR. KUEHNERT: Okay. Harvey Alter?

DR. ALTER: Mike, I think you know in endemic regions, it is almost impossible to distinguish
transfusion transmitted cases. They almost certainly --
you must occur but we just can't sort it out from the
background, but that makes it I think particularly
worrisome in a non-endemic area because we know the vector
for dengue is here, we know that people are coming from
dengue-infected regions, and we know we have a highly
susceptible population.

So I think the -- if dengue -- it's likely that
dengue is going to increase in our population and it's
likely that the transfusion transmits. So I am worried
about that particular agent for those reasons.

MR. NAKHASI: And Hira Nakhasi. Susan, I think,
on looking at your slides, the one which strikes me most
is the challenges. I think that's what we are here, to
address the challenges, as you pointed out. I think we
need to keep in mind for the discussion -- or maybe you
can illustrate you know a point on it now but later on in
the discussion, what we hear is so far yes, we may be able
to know the scientific and epidemiological knowledge about
a particular agent and may be able to, you know,
prioritize based on that.

But at the same time, this is a -- another
aspect is the public perception and where the science may not be yet firm. So I think the question here is not only that you have to prioritize, but the question is what is the responsibility of both public health agencies as well as the stakeholders? How do we respond to those situations?

And, you know, we -- because I think the question I'm always asked at many of these forums is how does FDA prioritize it, today chikungunya, tomorrow West Nile, and day after Chagas. I think what we need to get out of this workshop here, is there a process because that's the question we're always grappling with. And I think we need to focus on that during the discussion and as well as during this process.

So I think if you have thoughts now, but we could later on, postpone.

MS. STRAMER: I think that needs to have the wider discussion.

MR. NAKHASI: All right. So I can --

MS. STRAMER: I do have my thoughts. But I won't get into that now.
STRATEGIES FOR MANAGING EID THREATS TO BLOOD SAFETY: A HEALTH CANADA PERSPECTIVE

DR. KUEHNERT: Our next speaker is Dr. Peter Ganz. Dr. Ganz is the director of the Centre for Biologics Evaluation within Health Canada. The Centre is responsible for evaluating safety, quality, and efficacy of vaccines, blood cells, cell therapies and tissues, and also responsible for developing safety standards and inputting to federal government policies dealing with transplantation and transfusion.

As director, Dr. Ganz has been instrumental in driving forward several important blood safety initiatives for Canada, such as directives to control infectious disease transmission through transfusion and transplantation. He's going to be giving us perspectives from Health Canada on managing EID threats.

DR. GANZ: Good morning and I'd like to thank CDC, CBER, Dr. Nakhasi, Dr. Kuehnert and staff for inviting me to this workshop and to share the podium with a distinguished group of speakers. I'm trying to get this to move down, it's stuck.
Okay, this is really a reminder slide for me that the area of emerging infectious diseases is really quite a broad area and I think there's -- in the interests of time you have handouts of my presentation, but I'm going to miss a couple of them, because I think that some of the background slides because of -- Dr. Hughes covered many of the topics very eloquently.

I think there's a couple of key messages from my presentation today. One of them is that I think in terms of managing EIDs, I think communication is really a key, a key, and I want to just point out a couple of the areas I think that we can address perhaps in panel discussion in terms of how we share information about EIDs and approach the issue of EIDs in a global way.

Again, I think as part of that strategy, I think one of the take-home messages certainly from my presentation will be that I think one of the challenges that we need to take up really is how we manage EID -- EIDs on a global perspective and that is cooperatively. I think many of the infectious agents do not have passports and given some of the issues with increased global transportation and so on that we really need a cooperative
approach to managing EID risk.

I'm not sure there's any comfort for regulators or the public in trying to manage these kinds of things within national borders. This is an illustration from a Nature article, demonstrating -- nature, human nature, demonstrating that -- I think really highlighting that global warming is really something we need to really pay a lot of attention to, because I think as we heard this morning, a lot of the vectors that transmit infectious disease are in fact expanding or moving into niches that are becoming available through global warming.

To frame my presentation really, I've got two questions, key questions that I'll try and address. The first one is a Health Canada perspective on how we currently manage EID risks, and also what areas we can act on to improve the way that we manage EID risks. I wanted to mention that although the focus of the workshop here is on infectious disease risk, clearly within the blood system, there are other risks that are much broader than just EID issues and these include good manufacturing practices or quality risk issues as Dr. Epstein mentioned in his introductory remarks.
And also there are patient-specific risks to transfusion that need to be addressed as well as a very broad issue that certainly is important for us in Canada, and elsewhere, which is the availability of blood and blood supplies. So EIDs are important, but they're one part of the overall equation that has to be considered when we're talking about transfusion and blood safety generally.

Now, in terms of the broader issue of health policy and effective risk-management for EIDs, it really is based on having available good scientific evidence to make decisions about, but that's not easy. It's easy to say, but the question really then becomes is how -- how accessible are the data, and obviously there may not be data, and even if there is data, is it available at the time you want to make a decision? And those are two things I think that really have impacted us in Canada and I'm sure worldwide in terms of making effective decisions.

We do have within Health Canada an existing framework for managing risks such as EIDs, and necessarily as a regulatory authority, it has to be fairly broad to cover not just blood and transplantation, but broader
issues. We do have what's called the decision-making framework. I'm not going to go into a lot of detail that's available on our Health Canada website if you're interested. It is a process for managing -- identifying and managing risks to broader -- in a broader sense to health and again the framework applies to not just managing risks from disease, but hazardous substances, food, medical devices, drugs, tobacco, and other consumer products. And so this particular framework is -- exists and we use it to manage fairly generally risks in all of those areas, and it really is made up of sort of three areas.

The first one is to issue identification, to try and identify the issue and put it into context. A risk-assessment, a part which deals with assessing the risks and benefits, and lastly, the actual management part which is to look at the options that are available for managing a particular risk, selecting a strategy, implementing the strategy and also monitoring the effects of the particular strategy or the option that's chosen.

This is sort of a coalesced Venn diagram showing where we start which is identifying the issue and its
context and then moving to assessing risks and benefits, developing options, selecting a strategy and monitoring evaluations, quite important. And as Dr. Stramer pointed out, involved -- interested and effective parties seems to be a real difficult issue with this, because again what defines the public for example, and who do we involve and how do we involve them in a timely way, particularly when issues are happening at light speed often.

Now, at the heart of risk -- the risk benefits really of an issue are the heart of making decisions for the regulator certainly, and obviously risk-benefit analysis forms the basis of decisions on emerging infectious diseases, and again risk management is fairly broad, and again is related often to a particular perspective. So one has to be I think very careful with who we involve in decision-making, who is accountable, if there is a broad group of engaged stakeholders. And that's not easy.

I'm sure you've seen this before, the "Safe Blood Paradox." Certainly it applies in our area as a challenge for the regulator, and that is blood has never been safer, but safe is never safe enough and again the
public -- and certainly in Canada having gone through the tainted blood tragedy and having had a Royal Commission to look at it, this has become I think very important and I'll talk more about that later. I think the linkage that's important for us is -- as stakeholders is what is the linkage to broader health care costs, and what are our obligations as regulators. And yes, we want to -- we're never going to approach zero risk for blood or a transplantation, but how far should we go, and who is accountable for balancing the costs of trying to attain a near-zero risk, and how do we balance that and how do we take it into account in decision-making within the regulatory authority.

There are dimensions to risk, you know, previous risk, current risk, and future risk, and I think the real challenge is how much attention and focus needs to be placed on accommodating future theoretical risk with actions or interventions that we take. And also -- and again this is I guess perhaps a sovereign issue, and what are the consequences of errors in predicted risk.

And I think that that's a really important one because it really focuses our attention on how good we are
at predicting risk, and what -- and predicting and putting in place strategies for what happens if we don't -- if the prediction doesn't turn out the way we think.

Now in Canada, the question then is, you know, who is responsible or accountable for managing risk particularly for emerging infectious diseases and although the finger normally points at the regulator, in fact within Canada I think we have a fairly balanced blood system and I think nobody -- the regulator doesn't own blood safety, neither does the federal government. I think it's one really that is shared, shared responsibility, and certainly if the regulator makes a particular decision regarding deferrals or introduction of a test without the cooperation of industry to develop the test and the operators to actually operationalize the test, we're really not getting anywhere.

And so clearly within Canada we have I think a very good line of communication and a system for trying to address risks in a fairly broad way. Now, in terms of how we -- the recipe for approaching emerging infectious diseases and the factors that we consider, you know, are as follows. Published literature, and in fact I should
have had a bullet there for, you know, sort of gray area, web-based information, so it doesn't actually have to be, you know, published literature and a peer-reviewed journal that is a trigger for drawing attention from us.

Surveillance data is key. I'll talk more about that later. Certainly risk-modeling and bioinformatics, and Dr. Epstein touched on this in his introductory remarks, is becoming a very important area for us as regulators in terms of information -- a source of information for how we manage developed strategies.

Global experience, some issues obviously start elsewhere. We talked about SARS and Dr. Hughes touched on the SARS and the fact that things happen outside our borders and certainly the way that those issues are managed very early have an impact on how we respond. And certainly there are other considerations, and -- touched on by other speakers dealing with political or population-centered issues that we have to take into account.

The general formula that we have within federal government in Canada for managing infectious risks to blood really are -- fall into the following types of categories. Obviously there is an initial trigger,
identification of a possible risk to blood safety and that could happen through surveillance data, through our public health folks or globally. Characterization of donor-risk exposure and that's not an easy thing. Even though we talk about it as being important, it really is not easy. Exposure, common and endemic areas, endemic areas are changing with climate and ecology, and there's also mobility of donors as well as blood to take into account when we're considering characterizing the risks of -- donor risks.

They're obviously further assessments to donor risks. It can be informed through seroprevalence surveys, donor screening, and also developing sensitive and specific lab donor screening assays would, I guess, fall into sort of the, you know, the perfect scenario in the sense that following up on identifying issues that led to donor exposure and then perhaps testing down the road. But even in that area there are still some decisions that need to be made about whether or not selective or universal donor screening is an option, routine versus periodic or seasonal screening, and serologic or nucleic acid testing, which types of tests should be chosen.
Now, I've tried to review sort of in -- retroactively what we have done in Canada for the last 25 years in terms of blood safety. Obviously we're quite proud of the fact that we've done quite well in -- since the 1980s, since tainted blood in improving blood safety. In Canada we have very much improved donor screening. We've developed and have adherence I think to GMP and blood centers, which I think is very important, and will be the subject of a World Health Assembly resolution coming up next week.

We have a national surveillance program or haemovigilance in Canada. We have national standards for blood safety that include screening, processing, testing, adverse reaction reporting, and standards for transfusion services in hospitals, and we also have a national inspection program.

As well in the area of infectious agents, we -- and these are ones I think I've tried to sort of split them into ones that we've taken action on that are in the -- which are motivated in part by the precautionary principle. These are not, but obviously we have increased and are looking to -- we have a dynamic donor screening
process and so as epidemiology changes, we're quite able to change the donor screening process to adapt.

We implemented universal leukoreduction in 1998, and we've had -- we're introduced as has the U.S. nucleic acid testing for a number of important agents over the years. And again for -- we coordinated our West Nile virus testing with implementation in the U.S. in 2003.

Dr. Dodd touched a little bit on the precautionary principle. I've, you know, I've mentioned this under the banner of regulatory challenges. It is a challenge for us in Canada, because our Royal Commission, the Krever Commission did spend quite a bit of time talking about the fact that our -- a number of different players in Canada failed to act, waiting for additional scientific evidence to informed decision-making, and hence our application of the precautionary principle has been focused really on acting -- doing things before we actually have a complete picture. So Roger, the comments weren't considered by Justice Krever.

The precautionary principle is one that we have actually used to introduce donor deferral for variant CJD, simian foamy virus, and XMRV, and I can say a couple more
things about that later. This is a fairly busy slide and I don't really want to get into a whole lot of details about it, but what it does is really sort of summarize Health Canada's role as a regulator since the 1980s and where again we're looking really at a development that means the ABCs are really events and health issue identify as A, consequent action, B and health issue resolved as C, and you can see as you move forward in the chronology of event or the abscissa (phonetic) that I think certainly in the last 5 to 10 years we've done a much better job at identifying health issues very, very early and so -- early enough that I think it makes it easier for us when the actual real issue is hitting the road we're I think much better prepared and that again is a comment on haemovigilance surveillances we've set up in Canada as well as I think increased communication.

So I think we've gotten a lot better being able to predict risk in Canada. Let me touch on -- for a couple of minutes on the importance of surveillance in the area of emerging infectious diseases. It is integral to managing risks appropriately and the haemovigilance that we have set up in Canada really is an integral part of our
risk assessment process for blood safety.

Within Canada, we have a -- formerly Health Canada, we had -- our public health agency was part of Health Canada. We've since the SARS issue, we've split our public health group into a separate agency, and they have responsibility primarily for surveillance systems and we have quite a large number of surveillance systems for different kinds of infectious disease, and actually you can find a list of them at our -- at the Public Health Agency website.

With regard to blood, we do have a -- the haemovigilance system that we've setup in Canada is really made up of two parts. The first one is a Transfusion Transmitted Infections Surveillance System or TTISS, and we also have a -- I guess a daughter of the original TTISS called the Transfusion Error Surveillance System or TESS, and both of the key leaders in that area are in the room today, Dr. Jun Wu and Luna Bengio. And we owe them a lot of credit, and the level of surveillance is really extremely helpful to us as a regulatory authority in being able to devote resources to areas that have been defined through haemovigilance as being ones that need
prioritization or emphasis.

And without having to actually read this, it's pretty clear that surveillance systems are really important in improving transfusion and maximizing patient safety. Now, what are the current strategies that we have in place for addressing EID risks to blood safety? Obviously the initial one is to identify risks and threats and use blood donor deferral algorithms to exclude individuals or groups with high threat to safety ratios as an initial intervention, develop tests for infectious agents with no risks through transfusion if possible, and implement surveillance measures to assess residual risk to system following those two steps, although clearly we -- the surveillance systems are set up so that we can actually use them in advance of having to go through those particular steps.

Now, in terms of what we -- obviously the best solution to solve EID threats is not to transfuse blood or use blood and not -- I think that's an aspect that certainly stakeholders have -- are continuing to advocate to the regulator is that we should do more to promote blood conservation technologies, promote good clinical
practice for using minimal amounts of blood and also to look at technologies that could play a role in -- as blood replacement technologies. So those are areas I think that are still important and certainly the public is -- had been quite vocal about asking the Public Health and the regulator to continue to champion.

Ideally, and this is -- Dr. Epstein mentioned this in his introductory remarks. It would be the Holy Grail. It would be very nice if we could eliminate the current paradigm of identifying infectious agents, deferring donors, and developing new tests and it would be nice if we had agents that we could use that are benign that we could use to treat blood in a proactive way and not worry about long-term effects in patients that receive blood that could be treated with pathogen reduction technologies.

Now, how safe is the -- how good are we as a report card in Canada in terms of managing the serious risks? This is a, you know, a capture of an article from Sheila O'Brien in CBS. And I think we're doing quite well, certainly by standards for managing infectious -- emerging infectious diseases or existing ones within the
blood system. The rates are very, very low.

Now, what are the barriers that the regulator may face in terms of going forward with attainment of the Holy Grail and having new technology that is really at the forefront in terms of perhaps having a positive impact on managing EIDs? I think certainly there is angst on the part of regulators in moving forward with new technologies especially when the future is a black box. And again ultimately we would like to have more information about new technologies and their -- how they work and what the impacts are on patients down the road.

And again this deals to a large extent with how we -- the comfort level, there is really one of the general population, and it maybe different depending on the country that you're in, in terms of what is the risk-tolerance of the population, and as Dr. Stramer mentioned, what defines the public, and what is the risk-tolerance of the public?

Now, one of the areas interestingly enough, Justice Krever in Canada, the Krever Commission had 50 recommendations from 5 years of work and many millions of dollars and one of the -- the only recommendation that was
never implemented that Justice Krever put forward was an indemnification scheme. And I think that's really quite important in terms of a barrier that we can maybe eliminate at the regulatory level, and in terms of making decisions if we're -- if there is an indemnification for either adopting technology and moving forward recognizing that there may not be a lot of good evidence as to what the impact would be in the long term.

Now, again, is there applicability to blood systems? I -- you know, I don't know of any examples, but certainly in my area, in the vaccines area, we -- the H1N1 Arepanrix vaccine that we approved in Canada over the summer did carry an indemnification scheme from the manufacturer, and the government was able to cover the fact that there were some unknowns. We have a whole lot of clinical trial data to -- for this particular vaccine, but we felt that there could be a public emergency and that it was needed, and the risk of giving it would be less than not giving it. But certainly government is not a stranger to indemnification schemes, and perhaps this is something we can discuss a little later.

Risk-tolerance is a local consideration, but
local actions may have global impacts, and again Dr. Dodd mentioned this as well in terms of XMRV, the fact that decisions were made in Canada to defer individuals with chronic fatigue and obviously there are global implications and why did we do it, on what basis did we do it? And so there would be -- it would be helpful to have clarity around how that decision was taken and what it means for other jurisdictions.

So should there be greater international collaboration in managing EID risks and also the processes that we use to manage EID risks? What can we consider in terms of a vehicle or a process to look at managing things more on a global perspective because I -- as I said earlier EIDs are not owned by any particular jurisdiction, they're global. So within the blood area we have WHO which has done -- played a similar role in the area of vaccines and immunization, and in the pandemic. We have a Blood Regulators Network at WHO. There is a Global Collaboration for Blood Safety Group, and there's a Global Steering Committee for Haemovigilance.

So WHO has a number of different subgroups that are looking at blood safety in a very general way.
Obviously there are professional organizations, ISBT, AABB and others, and certainly there are regulatory jurisdictions and there's also networking, what I referred to as NGOs or networking partners, EDQM, Council of Europe, and the Pharmacoeplia. And really how do we coordinate managing EID risks among various interested parties? Should there be a need to do that? And I do think that there is, and that's one of my take-home messages. I just don't know how to at this point operationalize it and would be willing to hear what your thoughts are on it.

One other issue that I -- that certainly coming from our experience in Canada is that risk-management really is a multi-faceted area, and there are many different components of risk. In addition to health risk, there is financial risk for perhaps organizations that need to implement tests that may or may not have been mandated by the regulator, organizational risk, reputational risk, legal risk, and political risks. So I think that we have to be cognizant of the fact that we do have a number of different kinds of dimensions to the risk equation and that certainly the impact of these other
kinds of risks on the risks that we're considering within the blood area need to be considered and taken into account.

So who owns responsibility for coordinating multifaceted risk management and for decisions? You know, I would -- as a question I bulleted governments, regulatory authorities, industry and others and clearly I think the answer is all of the above, and again I think that this comes back to the communication slide that I had is that really we need to find a way -- better way to communicate amongst parties.

Now, what dimensions of the issue should involve global considerations? I think that's a really important point and one of the messages from my talk is I do think that global considerations have to be brought in somehow and because what we do in Canada has impacts elsewhere, what you do in the U.S. has impacts globally. And so I think that this is really -- EID risk-management is really a global enterprise, and I think we need to try and do that.

One other part of my presentation that I wanted to highlight is the high public expectations and both -- a
number of the speakers touched on the high degree of public interest in XMRV as an example. Information travels at the speed of light and obviously we're extremely well connected globally. There is worldwide exposure for issues, if not agents, and obviously challenges involving the public in decision-making. I think in the -- in this particular century we live in there is a -- I think there is a lot of -- they're very vocal, very informed public who do feel that they want to be involved in decision-making and how do we do that. I think that's a particular challenge for regulatory authorities in how we involve the public more in decision-making, and also an expectation certainly in Canada on the transparency of regulatory processes. In other words, how do we go about making decisions that impact the public and impact patient safety and be open and transparent about how we do that.

What about the way forward? I think as I -- again I am probably speaking in monotone here, but again I think international collaboration and cooperation is very, very important. I think we need to have stronger links with other governments and regulatory authorities to
manage EID risks. I think that you need increased networking of researchers and labs in the area of EIDs, so that you have also a better connection between people working in the field and as Dr. Hughes showed in his presentation this morning, clinicians working at -- or veterinarians working at sort of the grassroots level in the area of emerging infectious diseases, how do we better integrate data that they are exposed to on a daily basis.

And I do think in the area of blood safety global collaboration in managing EID risks is a -- would be a really, really good thing. I think right now it's not there. I think it's somewhat -- if it is there it's fragmented and it's not very well coordinated. So I do think that that's an area that we need to move forward on.

And this is my last slide and it was taken from an editorial in a British medical journal a while ago on "A walk on the wild side -- emerging wildlife diseases," and I think it really highlights the importance of a meeting like this focused on EIDs. Climate change, deforestation, pollution, pathogen evolution and the rapid global movement of people, animals, and animal products have all put humans at increasing risk of major
epidemiological shifts in existing zoonotic diseases in wildlife and emerging new ones.

There is no doubt that a unified multi-country strategy is needed to combat the increased threat of new and emerging pathogens to animal and human wellbeing. We need to be aware of every potential threat from the recent emergence of diseases such as avian flu and swine flu to the changing distribution of bluetongue virus. So you'd probably be asking what's bluetongue virus? It's an orbivirus. It has a high morbidity amongst livestock and actually it was -- about 10 years ago it was present in livestock in Africa and in the last 10 years it's moved to -- it's a major issue for U.S. livestock, cattle and sheep, and actually 2 years ago it was -- it had gone from tropical to semi-tropical and now is found in -- there was a case in Britain a couple of years ago.

And this seems to be a -- again fueled by global warming, but it just goes to show you that in 10 years you can go from one continent to global in a very short amount of time. So with that I think I'll leave you with a quote from one of my favorite U.S. presidents, and I hope that I've convinced you that in the area of EIDs, international
cooperation is really quite important. Thank you very much.

(Applause)

Q & A

DR. KUEHNERT: Thank you, Peter. We have some time for questions.

DR. KLEINMAN: Steve Kleinman. Peter, I -- obviously I got your message. It was -- you know, you made your take-home point, but I want to just press you a little bit on it, because I think it's, you know, it's a nice platitude, but I think it's really hard to achieve and the reason is something you alluded to. There's different levels of risk aversion in different countries because of past histories and the culture. And so I think if you look in the blood safety arena, you need to -- if you look at the countries who had the most political and legal fallout from "tainted blood" or HIV, you'll get countries like Canada, Ireland and France, and you'll see that these are the first countries -- these are the countries to act first when there's a new potential threat
and to put in more stringent measures.

And so how then do those countries who want to take interventions more quickly, how do they -- I mean, they communicate perhaps, although generally we find this out not through formal channels, but we find out that a new intervention has been put into place either by networking informally or by newspaper articles, but how do they convince their colleagues in other countries to do the same thing, or how do their colleagues who say it's time to wait convince people who are in a different kind of environment to take action?

DR. GANZ: Yeah, I think that's --

DR. KLEINMAN: I don't see the solution.

DR. GANZ: Yeah, no, I think that's an important point. So let me back off a little bit from the goal. I think you've stated the goal, okay, but I think really what it comes down to is understanding how the decision is made. I think if -- I think that's the really important point, because I think what's happening right now is when decisions are made, people don't understand how that decision was taken. So understanding that there may be differences in the decision, right, I think it's still
important to have a forum to discuss how the decisions were arrived at, right, so that should be the focus.

DR. KLEINMAN: Yeah, well, I definitely agree with that. I think better communication -- because maybe something that you've used for decision-making is a factor that would be important if somebody else understood the process you went through.

DR. GANZ: And I think it's an important point, Steve, because I think, for example, in the issue of availability of blood, and there maybe decisions that are predicated on having sufficient amounts of blood and that doesn't apply in a particular -- you know, another jurisdiction, let's say. So -- but understanding that the decision was made because of an issue like that I think is really the -- you know, an important step, because again we have to answer to our governments and explain that you know, they're relaxing criteria acts in this particular jurisdiction because it has an impact on the availability of blood. That doesn't apply in our context but.

So it's having a vehicle or a forum where we can understand the basis for decision-making at least so that we can actually -- we know why a particular, you know,
action is taken. I think that's, you know, not harmonization necessarily as an endpoint.

DR. KUEHNERT: Actually I had a question about -- and I've been asking almost every speaker about horizon scanning. And you know, Canada has one of the most sophisticated surveillance systems for haemovigilance, but it's a so-called cold surveillance system, and so by the time you get the data, it's -- and get it together and analyze it, it's very comprehensive, but it's months later, it's not a sentinel network. So I was wondering how Canada approaches horizon scanning in terms of gathering information and then disseminating that information throughout the structure?

DR. GANZ: Okay, I think Matt, I wanted to just -- I'll preface what I'm going to answer by saying that I think the surveillance system that we have set up is not perfect. It's evolving, and we understand from, you know, for adverse drug reactions for example, in a broader context that we're looking at capturing at most 10 percent of what's really going on. So our surveillance system is dynamic. We want to build more active reporting into the surveillance system that we do have. Right now I'm not
sure it's there yet. So it's a starting point, but it's an evolution as well, so I think that as we educate more frontline, grassroots-level physicians, clinicians about why it's important to report, then I think we're going to see a more robust system evolving, but right now we're still -- things are still evolving, but we're I think quite a ways down the road of having something that we can use in decision-making.

SPEAKER: Okay.

(Applause)

MR. NAKHASI: (Tape interruption) -- so in that process of identification, surveillance and prioritization, obviously it -- the next speaker's topic fits very seamlessly because the -- as we heard, risk management and risk assessment is a very important issue in prioritization of these EIDs. And I think I'll also -- we will also hear later on in the discussion who owns the risk.

And I thought -- I think that was a very provocative suggestion, how do we manage the risk. So in addition -- so therefore the next speaker is going to tell
us how do we do risk assessment in emerging infectious
diseases in blood. And our next speaker is Dr. Mark
Walderhaug. He is an associate director of risk
assessment, Office of Biostatistics and Epidemiology.

And Dr. Walderhaug is -- got his Ph.D. in
Vanderbilt University, held a postdoctoral appointment in
University of Chicago in the department of molecular
genetics and cell biology. He was a visiting assistant
professor at the University of Illinois at Chicago,
department of immunology and microbiology before joining

RISK ASSESSMENT: AN OVERVIEW

MR. WALDERHAUG: I'm very sensitive to the fact
that Dr. Kleinman mentioned he was between you and a
coffee break. And I am between you and a late lunch.

(Laughter)

MR. WALDERHAUG: So I'm going to try and get
through this in an appropriate manner. I want to -- I
think it's great that I followed Peter Ganz. I wanted to
say that my favorite Canadian prime minister was Pierre
Trudeau, but I don't have a quote for him -- from him. The other reason why it's appropriate that I'm following him is that he talked about the overall picture looking at the risk management issue.

And I think the one thing I want to contribute at this particular point in our series of presentations, which I think are really nicely connected in a interesting way, is the fact that as Peter mentioned, risk assessment is part of this whole process of coming to a decision. But there is a risk management component that the risk assessment feeds into.

And so rather than talking about risk management, which I think a lot of the speakers today have already talked about, the risk management -- both the risk assessment and the risk management part, I'm going to take a step back and just talk about the risk assessment part of this whole risk analysis process. And I think the reason why this is important is because a lot of the risk management part involves values.

And we've already had just a discussion at the end of Dr. Ganz' talk about differing values between different countries, between different constituencies,
between different stakeholders. What I think is really important is that before we talk about what we disagree on, I think it's really important for us to talk about what we agree on.

And I think risk assessment tries to get the science and what we know about with the uncertainty provided to the risk managers as clearly as possible so that they can take what the data are telling them based on the surveillance, based on the performance of the adverse -- the pathogens, and try and use that for us to agree on at those particular stage before we move on to trying to apply the values.

And I think that's what risk assessment is all about. So risk assessment formally started I think -- we've always done risk assessment, but the framework that I'm going to be talking about today, really sort of crystallized in 1983 at the U.S. National Academy of Sciences. It broke it up into four different parts.

One part was hazard identification, then there was dose response assessment, exposure assessment. And then the idea is to take those two components of how much people are being exposed to and what their response would
be to the amount that they were exposed and come up with a risk characterization.

I think that's our goal as -- from my perspective, from my job, to what I do for Jay Epstein is to provide him with a risk characterization, the best that we know about what's going on with respect to any of our blood-borne problems. And what we'll talk about primarily, I think, today is emerging infectious diseases in the blood.

So before I go into that, I want to just take a step back to what Peter Ganz was talking about, and put risk assessment in the context of what some people call risk analysis, and that is to look at risk assessment, risk management, and risk communication together at the same time.

And as Peter -- sometimes what they want to do -- we want to do is we want to look at, you know, all of the particular elements as being equal to one another and intersecting so that risk communication touches on both risk assessment and risk communication risk management. And some people, though, say that this is the risk assessment component, the risk management component, and
risk communication just entirely circles all that.

That there is all the -- I think -- and then we've already spoken today about the importance of risk communication as -- in this whole process. And what I talk about risk communication, it's not just between the risk decision-makers and the stakeholders. Risk communication in this context, this framework, is supposed to be two-way.

And I think a lot of the discussions today have been part of that risk communication effort where stakeholders say this is our perception of the problem, these are our values, you need to incorporate them in your decision-making. And this is an important part of this whole process on the part of the decision-makers. You've already seen this framework that Dr. Ganz mentioned with respect to the whole risk management process as well.

So there are many frameworks, but they're all similar in the sense that we try and have a functional separation between the science component, the risk assessment component, and the risk management part, which involves more than just the science. It involves a lot of values and -- as well, and also ways of dealing with
uncertainty.

So going through the individual steps. Hazard identification is generally easy with respect to our emerging infectious diseases, except maybe not so easy. And I think Dr. Dodd -- is gone -- and Dr. Stramer have talked about the problems of whether or not XMRV is really a risk and whether or not we've identified that hazard and the specific mechanism by which people are infected and whether it's a significant component of blood.

An example of -- another example of hazard identification is what our group did with respect to looking at Variant Creutzfeldt-Jakob disease and plasma-derived Factor VIII. And this is the work of Steve Anderson and Hong Yang where we were looking at the emergence of vCJD transmission via red cell transfusions back in 2003. And there was the concern that there may be vCJD in plasma-derived products including clotting factors like Factor VIII.

So the idea here is that this was the scope of the risk assessment, this potential for vCJD to be contaminating plasma-derived Factor VIII made from human plasma because of the fact that it's a matter of pretty
much legitimate concern. Because large pools of plasma are combined so that if there were one person infected, he would actually have a -- you know, a batch infected as a result of that infection.

And then this particular infection would then be, you know, either reduced or magnified depending on how it's processed afterwards. And so this was an unknown. And an effort was made to try and model this process to get to an idea of what was the level of risk associated with this particular product. And it was completed back in 2006, although it is currently being revised to incorporate new knowledge as most risk assessment should be, as new knowledge becomes available.

So the exposure assessment that was used in the vCJD risk assessment was basically to model the process. And the process included travelers going over to the United Kingdom and other parts of Europe and how long they stayed there. We don't have really good data for that, so most of that data was modeled not as a point estimate, but as a distribution.

And then using that distribution, we could use a technique called Monte Carlo Methods to estimate over a
large number of simulations, what that risk would be, what
the attendant uncertainty for each one of those processes.

So that is a key way of trying to stay away from
using just our mean estimates because of the fact that
although they're very convenient and they are our best
guess, they sometimes can give us a false sense of
security with respect to how well we know how much we know
about the particular problem. So here is an evolving
model of transfusion-transmitted babesiosis.

And what you see here with the diagrams not to
scale is we have our blood donors here and our blood
recipients right here where the risk is the fact that
there are babesia carriers. Some of them are symptomatic,
some of them are asymptomatic. And the asymptomatics will
donate blood, and this blood will go to the recipients.
And some of them will acquire transfusion-transmitted
babesiosis.

Now, there are two key unknowns in this model
that we're developing right here, and that is, you know,
what is the fraction of symptomatic to asymptomatic. Now,
you've heard Roger Dodd and -- talk about the American Red
Cross data that indicates that in some locations and in
particular states there could be 1 to 2 percent that are seroreactive for babesia.

Now, that is useful information, and we can model that data. But our problem is -- currently is to figure out exactly what the percentage of those that are asymptomatic who donate actually transmit a level of infectivity that will actually cause transfusion-transmitted babesiosis. So here is another key unknown here -- what's the infectivity of the blood.

Because some of those people with -- who are seropositive for babesia would -- will be -- have resolved the infection at some particular point, and they may not be infected. And some of them may be in a waning state of -- asymptomatic state where they still are transmitting babesia, but it's just not at an infective level. We don't know that. We don't know the infective dose for babesia in blood.

We can make assumptions and we will be making assumptions, but these sort of factors are the key components in trying to build this model to help informed decision-making. Other things that we might have to worry about is, is older blood safer than younger blood, for
example, will -- does the infectivity wane over a period of time.

And in order to answer those sorts of questions, we're going to need more data to address those types of questions. So another component of risk assessment is the dose response which I've alluded to the babesia model as well. And then another question is what does the dose response curve look like.

And what I have here on the slide is what -- is a standard sigmoidal response that is true for a lot of microbial risks in humans where you have a very low risk associated with low exposures, which does not increase exponentially as the amount of -- and let me just take a step back and say this is the concentration of -- this is the amount of dose of the pathogen here, and this is the likelihood or the response to the illness actually occurring.

And so you have here low doses -- very reduced cases -- likelihoods of illnesses, and then at high doses you have very likely illnesses. And the point that I'm trying to make here is that -- and it's hard to see, but there are lots of other dose response curves here for --
that are -- basically could be the true dose-response relationship.

And so sometimes it's important for us to take these -- use our Monte Carlo Methods to look at each one of these dose responses as a possible response of the pathogen versus the exposure. In other cases we might think of these as being individual dose response for individuals.

So some individuals are relatively sensitive, and some are much more resistant to others. So this might be used for us to model sensitive subpopulations. And as we acquire some of that genomic information that we've already heard about this morning, we can refine our models to make them more useful and truer in terms of its -- their predictions.

So the final component of risk assessment is to combine these exposure assessments with the dose-response assessment including uncertainties from both the exposure component and the dose response, and represent that in a comprehensible way for risk managers so that they can reach decisions that are based on the data as opposed to the gut impressions.
So what's different, I think, for emerging infectious diseases is that in a lot of cases we have much less knowledge about the dose-response component than we do for the exposure assessment, although we have uncertainties for those as well. So for emerging infectious disease risk characterizations, they're generally characterized by having a lot of uncertainty in the results.

And let me show you an example of that in the next slide here. Whereas this was for the Variant Creutzfeldt-Jakob disease risk assessment that was done back in 2006 -- and I have only a small part of a series of results to show here. And as you can imagine, these -- this level of information can be very overwhelming to both the risk managers and to stakeholders when it gets presented to them.

And it's a challenge to do this in a way that can be understood. And what's complicated about this risk characterization is that we have lots of extra information to model in here. And one of them was there was an epidemiological model for prevalence in the U.K. which affected the level of infection in travelers who traveled
to -- could have been infected or traveled to Europe.

And then we have a higher prevalence associated with surveillance of tonsils and of appendicitis (phonetic) in the U.K. which indicated that there was a much higher level of infectivity in the U.K. But in one case this was a prediction of the incidence, whereas this is a prediction of infectivity or a level of infection.

So we know the nature of Variant Creutzfeldt-Jakob disease is that depending on your genetic background you're more susceptible if you're homozygous methionine in codon 129 for the prion protein and less for the other components. So this difference might be a reflection of those differences in infectivity versus going on to a full illness.

And so what we have here is that using the lower prevalence model for a particular patient who received this particular dose of plasma-derived Factor VIII used in a yearly period. And this is the total number of patients who we estimate would have that level of exposure. That could be as low as one case of vCJD in a very, very long time.

And our uncertainty is it could be zero and it
could be a little but larger than this, but it's still extremely low. Looking at the different level of risk in terms of the infectivity as opposed to the prevalence, we have an estimate of -- it could be -- on average, the mean would be one vCJD case in every 35 years. But that's our mean estimate.

If we looked at our 95 percentile estimate, it could be as often as one case in every 8 years. So which level of risk a risk manager wants to look at is they have to make a choice based on the fact that there is a lot of uncertainty in these particular characterizations. But this is pretty much our best understanding of what the data are telling us with respect to that risk.

So as you can appreciate now, to characterize risk is -- in a way that risk managers can use in a productive way is a challenge for us. Part of the advantage, though, of modeling this in a very specific way is that in spite of the fact that we have relatively large uncertainties for a lot of our results, the advantage of doing this as a model allows us to check the sensitivity of the variables within our model.

And in some cases, this is as useful as the
results are for characterizing the risk to the risk managers. Because what I'm going to show you here is that this was a sensitivity analysis using the model where we vary the various components of our model and we look for its effect on the level of risk that gets predicted.

So the key variables in this model were the -- this is the reduction of the vCJD agent in the process of purification of the Factor VIII from the plasma. And so you can see that this particular component had the greatest impact on the risk characterization as opposed to the efficiency of our donor deferral policy, which if it were more effective, would cause the risk to go down by a very, very small amount.

Whereas if we knew more about the effectiveness of the reduction of vCJD agent in the Factor VIII, we could see a much larger reduction. If we had uncertainty, for example, with how much was being used per year, that could drive the risk up. But still, this is probably less important to understand than this particular component here. And in this way risk assessment can really help target the research that's needed to provide risk managers with better information.
So if we were going to put -- decide what component we wanted to spend more money on to do research, what our model is saying -- and our model could be wrong, but we have certain -- we try and make our models as valid as it can be -- is that we want to do more research on the effectiveness of the -- of our -- of the purification process to reduce the prion in the -- potential presence of the prion in the plasma-derived factors.

So the -- this was then. Right now, with the presence of new potential mitigations whereas filters are being developed that can -- that are being -- that specifically work on clearing prions from fluids, we might be able to come back to this and reexamine our important -- importance analysis and come up with a slightly different decision, but also perhaps reduced uncertainty in our risk estimates and maybe reduction in the estimate of the risk.

So I just wanted to touch on what the risk assessment does for the risk manager in the sense that -- to remind you some of the points that Peter Ganz made, that risk managers have to consider more than just the risk assessments. And I think it's better for us to talk
about those differences than to have questions about how the actual risk is.

And so I think it's really important for us to work on getting that risk assessment right so that we can have arguments about the proper things. The risk benefits are also considered in the risk management. And so the other component that Peter talked about was the presence of what is the baseline risk, how does the risk change if we change the various components.

So in the case of emerging infectious disease do we test everybody, or do we just test a regional area; does the risk change if we change the questionnaire, which -- what would happen if we had a test that had a higher specificity in terms of the ratio of true positives versus false positives and model other risk-reduction strategies.

So to try and summarize this again, if we were talking about the next arbovirus, we would be looking at whether or not there is evidence of transfusion transmission in this particular component. We would figure out -- we'd try and get information about what the effective dose is of the next arbovirus, and then try and model the exposure of both donors who would be exposed to
the arbovirus.

And then the likelihood of the recipients receiving -- becoming infected by the next arbovirus if they received contaminated blood, and then for us to again look at baseline illnesses and then start modeling what would happen if we were given several different mitigations to look at how much case -- how many cases of the next arbovirus would we be able to miss or avoid.

So again getting back to the risk assessment component here, what are -- what we're trying to do is to develop a transparent sharable understanding of the problem based on the data that are available. The challenge of doing this for risk managers is it becomes very complex to present this data to risk managers and to stakeholders in a comprehensible way.

We have the problem of dealing with data gaps and uncertainties. In many cases it makes it look like the risk assessment isn't providing very much value because of the large uncertainty associated with it. But it's better for us to communicate the fact that there is a lot of uncertainty than to give the false impression that there's a really -- that this is all really nailed down.
We're probably going to see us getting better at doing these sorts of risk assessments because technology is changing so that we can do our Monte Carlo simulations with much better hardware of many, many cores trying to examine our problems. And this is -- has real benefit to us when we try and develop a better perspective of the problem to communicate to the risk managers.

And we're getting more models to look at and then to build off of. And unfortunately, the negative trend would be the fact that's been already addressed today, about the fact that EIDs are emerging more quickly. So that's my presentation. That's the risk assessment component of this. And I'm ready for questions.

(Applause)

Q & A

MR. NAKHASI: Ready for questions, yes.

SPEAKER: One thing I wondered about as I looked at the variant CJD example is oftentimes the attention tends to be driven towards the highest risk estimate possible. So whether you say 95th percent confidence
interval, 99 percent, you're looking at that one in eight, that's the one that sticks in your mind.

MR. WALDERHAUG: Right.

SPEAKER: How do you avoid that in terms of risk communication and avoid the sort of syndrome of -- sort of model where you look at the 95th percent confidence interval at the highest point, then for the next step you go again to the 95th, you go to the next? And then before you know it, everyone's going to have the disease in question at 100 percent risk rate.

MR. WALDERHAUG: Right. I think that's particularly a problem not only to risk communication, but also as we develop the model is to not incorporate a creeping conservatism as we develop a model. And so we might be tempted to say, well, we know it's below this as opposed to actually trying to figure out where it might be or to model that entire range of possibilities so that we can understand the risk might be lower than we think.

Now, as far as the risk communication aspect is concerned, I think that's a challenge for us because we don't really have an answer for that. Because various constituencies will look at the elephant and see -- you
know, they'll find the part that they want to, you know, hold and say this is what the elephant is.

It's, I think, the risk managers' responsibility to work with the risk communication experts to try and communicate that, okay, there is uncertainty here and we don't know the full answers. On the other hand, as we look at these answers and we've incorporated what we think is an accurate representation of what we think the risk is, the bulk of the risk is at this particular stage as opposed to the higher stage.

So I don't have a good answer for you, but it's clearly an area where we need to work harder.

SPEAKER: It's really two different questions. Thank you for breaking that down for me.

MR. NAKHASI: Mike.

SPEAKER: (Off mike). You know, with Chagas now in hindsight we'd say with the look-back data that we've generated, we might question whether a decision to screen had been indicated. But you know, the early years of the studies by David Leiby in Red Cross, they showed donor prevalence, and you know, some level of parasitemia.

And the experience from South America with fresh
blood -- and instead of doing a controlled, you know, transmission study, disease outcome study, the decision was, well, we can't do any more of that linked research type of stuff because it's unethical. Whereas to me, it's almost unethical from a, you know, policy perspective to not get the answers to those critical questions.

And we're at the same point now in dengue. There is sort of an unwillingness to -- you know, to sort of bite the bullet and save some blood, get some pre-post-transfusion samples and really try to answer the questions definitively about transmission rate and disease penetrance.

MR. WALDERHAUG: Right. Mike, you're getting into the risk management component which I'm -- you're absolutely right. I'm not going to minimize your point. My point would be that risk managers have a really tough job. And sometimes they have to make decisions based on the available data that they had at that particular time.

And it's really incumbent upon the risk assessors to do as good a job as they can to give them what the data are saying that particular time. But the risk assessment can't help us if we don't have the right
data and -- where we can't wait for the data. So your concerns are absolutely valid.

But risk assessment I don't think is going to be able to address those particular questions. Risk management will have to do that.

MR. NAKHASI: (Inaudible), please.

SPEAKER: The issue -- risk management is certainly what drives a lot of that, but because -- certain step -- I have focused more on the earlier part of your modeling and how you make these initial assumptions. And this is an unregulated process, that is, how do you decide. Because there's -- certainly you are going to do a risk assessment in the absence of perfect data, otherwise you would have made the decision we don't need your department.

(Laughter)

SPEAKER: So -- but -- so what are the mechanisms that we can have to make those assumptions more compatible and more -- with reality and not driven by the values that people are trying to insert into the whole risk-assessment process?

MR. WALDERHAUG: There are a couple of points
there. And I think you raise excellent points there that part of the reason why risk assessment is separated from risk management is to provide that element of not necessarily having the people who are making the decisions controlling the data component so -- the analysis component so that there is a functional separation, although there must be good communication between those two.

Whether or not we risk assessors get it right at the very beginning, I think is supposedly caught at the stage where we are communicating to the stakeholders what our models are. And at that point we invite the feedback to say, well, look, this is not the way that we understand the exposures to be, and we have this data here that I think would be very useful to you in refining your understanding what the problem is.

And I think that's exactly what the risk communication is all about that I was alluding to with respect to the two-way communication so that in that very early part of the model it could be wrong, but we shouldn't be making -- you know, unless factors are driving risk managers to come to a decision more rapidly.
than they would like to, that there is a vetting process by which these models are communicated, shared, feedback is obtained, they're modified based on that feedback and they come to a truer value.

So it's -- your points are excellent.

MR. NAKHASI: All right. So I think -- I would like to take this moment at this point -- thank you, Mark, and if there are no more questions --

(Applause)

MR. NAKHASI: -- both myself and Matt would like to thank all the speakers this morning. Speakers -- we had an excellent presentation from each one of them, and at least we now have some ideas where the discussion is going to go starting from identification that is horizon-scanning, to surveillance, to prioritization, to risk assessment, and then finally the decision is the risk management.

So I think we will reconvene at 1:45 -- is that -- Jennifer? And we'll have lunch now. Thank you very much. Bye-bye.

(Applause)

(Whereupon, at approximately 1:05 p.m., a
luncheon recess was taken.)
SESSION 2: TOOLS TO ADDRESS EIDs

DR. ALTER: Okay. You did pretty good and get back from lunch. Thank you. So as I mentioned at one of these sessions previously, we have for the last few decades gone through the gates of hell. It all began with Watergate.

(Laughter)

DR. ALTER: And then we had to run Contragate (phonetic). Then we had Enron-gate. And now our minds are totally consumed with mitigate.

(Laughter)

DR. ALTER: Mitigate -- I looked this word up, because we -- I think it's the most commonly used word at any FDA meeting. And it means to make or become less severe, and comes from the Latin word mitis -- to soften. So our goal is to go soft on blood recipients by going hard on viruses or other infectious agents, particularly
those that are emerging or reemerging.

However, in the setting of an already very safe blood supply, while one can imagine that we could get even safer, the push to achieve that is if you would mitigate it by our comfort zone, our current comfort zone and by the high cost and increased complexity that might ensue from these new interventions.

So in this session we're going to discuss two relatively advanced approaches, namely pathogen-reduction or inactivation which will be discussed in philosophic terms by Ray Goodrich, and then pathogen microarrays discussed by Clark Tibbetts.

Now, microwave -- microarrays, although they offer the potential for testing multiple agents -- multiple reemerging agents at the same time, they, by their very nature are not preemptive and they cannot prevent a new agent from hitting the blood supply. It first has to cause disease and then be molecularly characterized.

These talks will be followed by an update on mitigation of prion-associated diseases by David Asher. Prions, unfortunately, do not render themselves to either
pathogen-reduction in this current technology or to microarray analysis. So in the end, I want to remind you that comfort is a very tenuous thing that can change dramatically in one infectious moment.

And I also want to give you the words of William Murphy who I tend to quote. I like the way he says things. And he said we are always one mutation or one vector change away from the next infectious threat -- that -- I like that sentence. So far, these emerging or reemerging agents have been reasonably handled since HIV.

But what if it is a new agent with devastating consequences such as HIV? That is why a preempted pathogen-reduction strategy is so much more appealing than our current reactive strategy to eliminate threats. So I end my introduction by adding that the road to pathogen-reduction, to innovative pathogen arrays and to prion-prevention is a very arduous and treacherous traverse.

There are many bodies and companies already strewn along this path. And we enter this session hoping that there be no more bodies, and that before I shuffle off this mortal coil, that one of these new approaches will be endorsed and embraced not only by the FDA but by
the blood community at large. I think we need to all get together on this and bring something to bear.

So with that, I want to introduce our first speaker, Ray Goodrich. Ray is the chief science officer for CaridianBCT, a division of BCT Biotechnologies. He is really in charge of research and development, and he's been in this field a long time. He's been awarded over 50 patents in the field of pathogen-reduction. And he along with Larry Corash (phonetic) are the two main movers in the pathogen-reduction field.

And I applaud their dedication, and particularly their perseverance in a very, very difficult arena. So Ray.

A BALANCED APPROACH TO BLOOD SAFETY: A POSSIBLE ROLE FOR PATHOGEN REDUCTION TECHNOLOGY

MR. GOODRICH: Can everyone hear me? Can everyone hear me? Trying to move it a little closer. Well, thank you very much, Harvey, both for the invitation, for the introduction. Jerry, thank you as well. The organizers at the FDA -- I want to thank them
for inviting me to participate in this workshop and the symposium -- very honored to do that.

I've heard pathogen-reduction described as the Holy Grail. I think that's a very appropriate analogy. I could tell you, after 20-years-plus of working in this area, it is very much akin to a religious experience, one that requires a tremendous amount of faith. As a self-proclaimed pessimist, I have to tell you that's often a very difficult proposition. I have the fortune, however, of being a very optimistic pessimist.

(Laughter)

MR. GOODRICH: So I'm going to speak to you today about some of the experience and some of my own personal insights in this area over that last 20-years-plus. Want to first of all start with a disclosure. I am an employee of CaridianBCT Biotechnologies. The organization that I work for is developing technology or product in this area.

The views and opinions, however, that I express, are my own. I am not trying to represent an industry; I am not trying to represent the company. As I say here, in many cases, my views may actually be contrary to the views
of my employer. It's a credit to them that they allow me to come here and speak my mind. I'll let you judge where those two may diverge.

I was recently given a book on leadership to read. And one of the messages in that book was to always try to find something good in the things that you do, or the things that you're involved in. And I actually found this quote in the book, from Shakespeare, which I thought was also appropriate in terms of the context of the discussion that we'll have here today about pathogen-reduction technology.

I don't list the book that I got this from, because unfortunately, this was the only good thing that I found in it.

(Laughter)

MR. GOODRICH: But it was worthwhile. When I first started off -- I like to tell people that I started off with a SBIR grant to the National Heart, Lung, and Blood Institute. This was back in 1989, and we received $49,786 -- I remember down to the penny what the amount was. And we had fully set out with the expectation we would have the situation and the problem resolved within 6
months.

Needless to say, it's taken a little longer, and we've been faced with challenges. I think with all projects you start off with a set of expectations about what you're working on is able to deliver, or will be able to deliver.

And certainly, that has been the case in pathogen-reduction technology, where over the years -- or at least starting off -- what I've heard and what I've observed as the claims or the hopes for these technologies, is that they would carry out their action without having effects on cell or protein quality, that everything we use would be completely natural, derived from mother nature, that all pathogens would be eliminated, that it would easy to do this for all products -- red cells, platelets, plasma -- and that the costs were small, and that they could be offset by cost savings that we get from other interventions that we might not have to employ.

Now, the reality is -- have been somewhat of a different story. There have been measurable changes in cell and protein quality as a result of carrying out these
processes. And much of the work that we've done over the last decade or more is to evaluate what those changes mean or represent from a clinical standpoint in patients who receive these products.

Agents may be added that are not normally common blood additives. I'm a chemist by training, and I have to say, sometimes I shudder when I think of the things that are being put into blood or the processes being applied to blood in the goal of making them safer. Not all pathogens have been eliminated. I think you heard that earlier.

I think effectiveness against most of them, if not complete, has at least been demonstrated. But there are some that resist the inactivation processes that have been proposed. Process control and product type is often crucial. Narrow ranges of cell concentration, plasma carryover levels -- whether it's done in additive solution or 100 percent plasma -- incubation times, et cetera, are very important in making certain that these processes are as effective as they are intended to be.

And then obviously, these processes are going to add cost. It's often been belt suspenders and a rope, just in case, to keep the pants (phonetic) elevated.
I also want to say, however -- you know, again, my perspective on diagnostics in the blood industry is one in which -- and having observed this from afar for a while, is that I think the expectations there have been very high as well -- that we could test for any agent, that testing wouldn't affect blood product quality or safety, that it's very easy to develop new tests quickly and implement them easily, and that the cost of these additional tests would be small, and that they could easily be offset and justified.

And although incredibly successful as an approach, there are some realities, some harsh realities that we have to come face to face with there as well. That includes that there are limitations on what we can detect. The time required for testing might extend quarantine periods and reduce product quality as a result as you use older products.

It takes time and money to isolate and identify new agents, to develop appropriate tests, and to demonstrate the effectiveness to the required standards that we've established for performance. And these processes are going to add cost and logistical complexity.
In an incremental fashion, that eventually is going to become unsustainable.

So I want to talk a little bit about risk analysis. The last presentation, I thought, was excellent; it raised a lot of very important points. But I want to do this from a slightly different perspective. And this is from an industrial perspective. What we face today in the diagnostic industry, to some degree, is an average of cost to develop a new test and put it into the market is about $30 million.

And that may range anywhere from $20 million to $100 million from the concept to full implementation. For new PRT methods -- and this information is available both in the public domain and from personal communications -- the average is about $500 million per method. That's part of that long, arduous road that Harvey was talking about. It ranges anywhere from $100 million to greater than $1 billion from a concept to full implementation.

Now, the one thing that I could tell you about in terms of -- again, from an industrial perspective is that the people who invested this money want it back.

(Laughter)
MR. GOODRICH: And in fact they want a lot more than what they put into the investments in these areas. And so just as the blood banking community, the insurance industry, and government health care reimbursement groups have to do cost analysis on new technology, believe me, the industries who develop these processes also have to do the same.

And that's why I think it's becoming increasingly difficult when you have seasonal or regional outbreaks of diseases like dengue fever, like babesia to find organizations that are willing to support the development and implementation of test methodologies to carry out both the surveillance as well as the screening of donors.

So what is the industry's challenge? If you want to stay active in this field -- myself and many of my colleagues both in my organization and other organizations, didn't enter industry just because we wanted to make a lot of money. In fact, if that were the reason, many of us including myself would probably be very disappointed.

We did it in part because we believed that this
is something that we can provide back to the community from the development of these tests from a blood safety perspective. And so the challenge is to continue to find ways to fund and support these activities, given the constraints of the economics of the blood industry and the desires of the investment community for rapid financial returns.

I mentioned about people wanting the money back. I'm often asked that question every other day -- when do I get it. I think there's also an issue of perceptions and realities when it comes to a risk assessment. The perception is that everyone wants safer, better blood.

I've not met any individuals in the blood banking community, in the regulatory environments from the conversations that we have, who say that this is not a goal that we should strive for. I sincerely believe that everyone wants this. But no one wants to take the risk or incur the cost of new approaches to achieve this in the absence of either a crisis or a major push by the health care community or the public at large.

And I think that perceptions can become reality only if costs are low. And I'm not just talking about
monetary cost; I'm talking about the cost in terms of the effects on products, the availability of products that go through these processes.

From a regulatory hurdles and commercial realities perspective, regulatory bodies are tasked with regulating the ultimate blood product that results from these processes as a biological or a drug so to speak. They insist upon a large amount of clinical evidence that the ultimate products are safe and effective, and I think that we can all be grateful that they do.

The method used to treat or test blood is appropriately classified as a medical device, and it's sold into a community which primarily exists as not-for-profit agencies. And so there is a cap in terms of the pricing structure that companies can obtain as a result of introducing these technologies. And that's a very real factor in considering the introduction of these new methodologies.

And so the issue of the barriers that are in place to entry into the marketplace become a very important component when evaluating this from a risk perspective as well. I went back and I actually saw this
in another book. It was -- I'll tell you what that book was, because I found a lot of good things.

And it was Malcolm Gladwell's book, *What the Dog Saw* -- a collection of his essays that appeared in the New York -- the *New Yorker* magazine over a number of years. And he actually referred to this, and I went and looked it up -- Kahneman and Taversky's Prospect Theory. It's a model for risky choice.

And what this describes -- Dr. Kahneman is a professor who received the Nobel Prize; he received it, Dr. Taversky passed away before he was able to receive it -- Nobel Prize in 2000. And he's an economist at Princeton University here in the United States.

Again, looking at preferences related to risk are reference-dependent. How do we make risky choices? It's not just a matter of the numbers that we face or the statistics, but the context in which those decisions are made. And the reference point is the current state or condition against which change may be applied.

So I'm going to give all of you a test. And you don't have to raise your hand, you can write your answer down. But this is a -- you're participating in a Nobel
Prize-winning test. So you should be very excited. Would you accept this gamble? A 50 percent chance to win $150, or a 50 percent chance to lose $100 dollars. Would you accept that? Yes or no?

Scenario two. Which would you choose? Lose $100 with uncertainty, or a 50 percent chance to win $50 versus a 50 percent chance to lose $200? Now, when they gave this test to a large body of individuals who responded, the vast majority would not participate in the gamble of scenario one. But when they were faced with a certain loss, they would take the bet.

And if you look at this from a traditional Bernoullian -- and you could ask one of the statisticians what that means -- perspective, the factors that are associated with this -- probabilities are about the same in both conditions. So it was the inherent situation of facing absolute loss that made the risk worthwhile.

So the question in terms of pathogen-reduction is -- and blood safety, what's our perspective. Do we operate under scenario one or scenario two? And I think as you've heard earlier, that the answer to this question may vary depending upon the geography or the point in time
that we find ourselves. And it may be more than just what the mathematics tell us the answer should be or needs to be.

So what are the options while we wait for an answer? Well, we could wait for epidemics. And I think Celso Bianco told me in December when I said this, that I threw a cold bucket of water on the proceedings. I said that I thought that for the decision to be a straightforward one, it had to be an epidemic not like the West Nile virus or babesia or dengue; it had to be the equivalent of an HIV epidemic.

We had a life-threatening situation, and there was no other choice to be made where you face definite risk. Lobby public opinion. And you will see groups that are doing this, that push for those particular groups we heard about earlier, to promote particular interventions. Whether they be diagnostic or be pathogen-reduction technologies, this goes on, to try to force decisions to be made in one direction or the other.

Or we can address the concerns over safety and efficacy via large-scale trials and investment in development and surveillance efforts to stay ready and
capable of responding. And there are several problems with this; the expense, you can never prove a negative. Prove to me that pathogen-reduction technology does no harm and the time that it will take to do that.

So is there an alternative? And these slides -- I actually borrowed, the next two slides, from a gentleman by the name of Johannes Blümel who's with Paul-Ehrlich-Institute. He did this presentation a few years ago at the IPFA/PEI meeting in Europe. Talking about the three barriers that might exist -- donor selection/exclusion, testing, and inactivation or removal technologies, there are pros and cons to each one of these.

There are benefits that each one of these introduce, but there are also downsides or limitations that they have in terms of effects that they have on blood product quality, on availability of blood, and nothing is perfect.

I think again in the blood industry, the perceived cost for implementing PRT, the message that you often hear, have hitherto been countered with a theoretical benefit of lower infection rates and the potential of eliminating some current tests or donor
exclusions. And that's what the idea of trying to achieve cost-neutrality with cost-reductions that offset the price of new technology.

And I think one of the fundamental questions is, is this fundamentally the right approach. Obviously, combining methods offers advantages. Use the strengths of both approaches to offset potential individual weaknesses that they may have. It combines a rapid response to new emerging agents with longer term, more complete resolution.

Like to ask this question. Would we be looking at XMRV and babesia in the same context that we are today if pathogen-reduction technology was in place? And I'll come back to that a little bit later. Well, let's look at this in terms of the individual agents that we may have to address.

Few years ago, I was walking the hallways at an ISBT regional conference in Europe. And someone shoved a flier into my hand. And it was advertising a symposium, and the title on it was, "You can detect or you can inactivate." And when I read this, the first question I asked is, is this statement really valid, is that right.
You can detect or you can inactivate? Is that true?

And so we set out -- this was about 2 years ago, I think, 2 or 3 years ago -- and I recruited some colleagues who are definitely much smarter than I, including Brian Custer and Mike Busch and Shawn Keil who's a microbiologist with our group. And we reviewed this from the standpoint of what defines adequate pathogen-reduction performance for transfused blood components.

This is actually an article that's been accepted, a commentary in Transfusion that's currently in press. And what we looked at in terms of viruses was the idea that what we know about viral dynamics when an individual becomes infected is that you have a period during which the viremia goes up. Initially at the very low viremias, you have what's called the window period.

And that's primarily from the point of detection where the virus might not be able to be detected, but it can certainly be infectious during that period. There is a ramp-up phase which is associated with the rapid proliferation of the virus in circulation, hits a peak viremia.

You get immune system resolution of infection in
many, but not all of the diseases to which individual is exposed, and in some cases a chronic phase viremia which may be characterized by a certain level of residual viremia that's -- can be monitored or measured throughout the course of the individual's life. And it can resolve itself completely.

When you look at window period from a diagnostic standpoint there -- and that's a slide borrowed also from Mike Busch -- there were different generations of testing that were put in place, different types -- originally HIV antibody testing, because you had to wait for antibody to become present and detectable.

There was about a 22-day window period from time when an individual was infected, to the point at which you could detect antibody in circulation. P24 antigen testing dropped that window period down to about 16 days. And with mini pool-NAT and ID-NAT testing, we dropped the window period down to 11 days in some cases. This is for HIV. I think with hepatitis it's as low as 5 days in some cases.

So there's been considerable improvement in closing the window period, though it is not completely
closed by these interventions. And I think evidence of that appears even with West Nile virus, for example. This is something I pulled out of an AABB newsletter back in November 2009, the CDC indicating that clearly there are cases where viremia is very low.

It's undetected by conventional testing or by mini pool testing. And hence more elaborate interventions may be required in order to find these infectious units when they're present in the blood supply. It varies depending upon the agent.

When we're considering the risk-analysis profile, it's not only a matter of understanding the viremias and where the virus titers that are associated with disease transmission occur, but it's a case-by-case basis in many of these situations. You can't apply the same standard or the same model to every agent.

That's different, for example, for HIV, HCV, and HBV than it is for West Nile virus or for cell-associated viruses such as CMV, EBV, or HTLV. So it becomes a very complex proposition to be able to get a full handle on what the risks are that are involved with this. The issue of dose, as was mentioned earlier, is also important.
We measure things in terms of genome equivalent; that means that it's there. It doesn't necessarily mean that it's infectious. And so what is the infectious dose that's associated with the presence of these agents, or the minimum that's required to transmit infection. These are some examples.

These are all in the article for West Nile virus and real data that was captured from actual screening of individuals who were infected with West Nile virus. And you could see that it peaks with a viral load -- genome-equivalent load of somewhere around 5 logs, around -- somewhere between 0 and 10 days. And then there's a resolution of the viremia in the subsequent period of time. And it varies from individual to individual.

Hepatitis B virus. This again is some real data. You could see titers in terms of genome equivalents that are as high as 9 reaching as high as 10 log genome equivalent per ml on these situations. And again, the viremia can possess for a very long period of time.

And hepatitis C virus where you don't see the resolution in these cases to the viremia, where you can see levels of hepatitis virus that are still at very high
levels throughout the course of infection in these individuals.

What does a PRT window period actually represent? Well, with detection, the issue is finding something that's there in very, very low levels. With pathogen-reduction technology, the issue is can you inactivate everything that's present in the unit. And if you can inactivate it completely, what do you leave behind, and what does that mean relative to infectivity.

And part of the argument that we posit in this commentary is the idea that what you do with PRT as you move the window period from those early low-level infections to window period that's associated with high-titer viremias that are present in circulation.

And the level of inactivation that you achieve -- just like the level of detection limits that exist with tests, the level of inactivation that you achieve dictates how broad that window period might be in terms of days during which individuals are infectious and could transmit infection.

Obviously, a way to close the windows, keep the doors shut and barred, perhaps, is by using the advantage
of pathogen-reduction technology to deal with low-titer infections or low-titer viremias and use the ability of nucleic acid testing or serological methods for that matter to detect agents that are present in very high titers.

It's an orthogonal approach in that you have two independent methods which rely on different physical techniques to allow you to extend the safety aspect of the product that you're transfusing. Now, how do we offset the costs and the complexity that are associated with -- if we combine methods in this way? Well, could we reduce deferrals if we're using tests -- testing combined with, in the appropriate places, inactivation or removal strategies?

Again, come back to something I said earlier about the change in deferrals. Donor deferrals are not cost-free. There is a cost that's involved with recruiting these donors. There is an availability of the products that is associated with them. So the decisions, obviously, to defer donors is not an easy one, yet a necessary one in some cases.

I think as we heard earlier -- and this again is
from an AABB newsletter in April -- there's been a
deferral now for XMRV virus. There's also been a deferral
in Australia and New Zealand following the lead that
Canada took. Now, these are countries in which pathogen-
reduction technology does not exist today. And again I
want to come back to that question I asked earlier.

I think we have an opportunity to envision -- is
the perception in countries where pathogen-reduction
technology is being used today for components, is the
perception going to be the same. Will we see deferrals be
put in place, or will those come later after we have the
time to collect additional surveillance data, assuming
that we have a protection mechanism already in place. I
think it will be interesting to see how that develops.

I'm going to skip through some of these slides.
But I think as complex as the issue of viruses in blood
are, bacteria becomes even more complex just given a
simple fact that bacteria grow when they're in blood
products. And they grow at varying rates. This is an
example of a growth curve for E. coli in tryptic soy broth
at 22 degrees.

In terms of defining adequate pathogen-
reduction, I will tell you that if you achieve 6 log
inactivation of E. coli, it's irrelevant. Because if you
have 6 log of E. coli in the blood product, even if you
inactivate it, you probably have a sufficient amount of
endotoxin that the transfused product into a patient is
going to cause a reaction. You haven't solved the
problem.

The issue is being able to inactivate very low
levels of bacteria that are present, and keeping those
products culture negative during the entire course of
their storage, or at least at low enough titers that they
don't induce transfusion reactions when they are infused.
This is an example of some work where -- just to show you
it doesn't only occur in tryptic soy broth but it occurs
in blood.

This is -- these are some studies that we've
done with whole-blood products where we've looked at the
growth kinetics of this case, bacillus cereus comparing
treated and untreated products. And again, the goal here
has not been to achieve high levels of inactivation, but
to maintain the products as culture negative to the limits
of detection that we can quantify that that were the
course of storage.

This is actually the subject of an article, was published in Transfusion last year where we set up an internal model where we could evaluate the effectiveness of both screening using culture method, as well as by pathogen-reduction technology method. And we looked at about 22 different strains of organisms, some of them different species or strains within the different species -- genus and species of organism.

I think another experience I've had is that -- in doing this work -- two, really -- it's very easy to show 100 percent effectiveness. All you I have to do is pick the strains that don't grow in blood. So it's very important that you characterize these in terms of describing the models.

The second thing is when we say we're effective against staph epidermidis or staph aureus, if you go to just the ATCC catalogue, you'll see there's probably about 40 different strains in there. Do you mean all 40 of them, or just the one or two that you happened to test? What we tried to do in this model is to really evaluate a broad spectrum of these agents, those that were both
resistant as well as less resistant to the processes.

This is really the summary table that came out of that data where we compared the effectiveness level that exist with -- reported in the literature from the American Red Cross and other groups -- Irish Blood Transfusion Service -- the effectiveness with bacterial screening and testing using different methodologies against pathogen-reduction technology.

And whereas we were able to reproduce, at least with this model, the kind of observations that have been made in real life with bacterial testing and shown an improved performance with pathogen-reduction technology, you'll note that none of these methods give you 100 percent efficacy, at least in our hands in terms of dealing with the bacteria strains that we evaluated.

Why do these failures occur? With culture methods you have stochastic sampling; basically you're taking a small aliquot out of the large. And unless we're going to test the entire unit, there's no guarantee that the aliquot that you take out is going to have the contaminant in it.

And then you also have very low initial titers
at the point of contamination. These are -- maybe 100 CFU in the entire product -- not per mil -- or less. I think our studies indicated maybe as low as 5 to 15 CFU per mil if you believe the model studies that we've carried out. With pathogen-reduction technology there may be strain-resistance to the photochemistry.

These organisms have developed ways of being able to deal or neutralize many of these agents, or binding to platelets or shielding may be occurring. There's actually a variety of work that's going on. Some of the early work by Clarkson and White, I think, was really fantastic work that was done looking at binding the bacteria to platelets.

Some work in collaboration -- much of this will be presented at the ISBT meeting this year in Berlin and at the AABB meeting in Baltimore. Question that we really developed a hypothesis that we've been testing last several months in collaboration with our colleagues at the Japanese Red Cross is what happens to these bacteria that escaped the pathogen-reduction system.

And we've used the model -- was actually developed by Azy Pharmaceuticals (phonetic) in Japan to
test against an agent, the staph aureus species that produces an enterotoxin B. And much to my surprise, what we're able to see is that although there are surviving bacteria at significant levels in these products, we see a distinct difference between the treated and the untreated.

And I'm using this to illustrate the fact that a log-reduction target per se may not necessarily be the only story that needs to be told relative to the effectiveness of these technologies. And so evaluating them in these -- in this context is something that again represents a very difficult proposition.

For parasites in blood products, they're often resistant to detection normally in low concentration in the peripheral circulation they can hide inside other cells and make detection more problematic. It's often an all-or-none proposition. I think some of the studies that have been done were done in collaboration with David Leiby's group at the American Red Cross.

You could leave as little as a single survivor behind, can lead to an infection at least in the animal models that we've evaluated. There's an increasing risk unlikely to go away. Changing climates and habitats
introduce increased risks. And travel, commerce, and vectors are modulating the frequency and the amplitude of these events.

    I like to quote Willy Murphy too. And one of the things I've heard him say is that he cannot control the global trade in used tires, but he has to deal with the consequences that that introduces by bringing new vectors into the community. So I want to use the teeter-totter analogy, I really like it. I'll tell you why later.

    There's a precariousness that's associated with teetering and tottering. The precariousness of blood safety -- you've seen this list, and I just tried to capture a variety of different agents that are on here. Agent X, Y, and Z are the topics of the next three workshops. They don't know what they are yet, but I'm sure that they'll be out there.

    And other people's DNA -- I am of course referring to white blood cells, potentially even to mitochondrial DNA if you believe some of the more recent nature articles that have been out there. And shame on you if you thought I meant something else.
Pathogen-reduction technology -- and one of the things that has attracted me to spending time in this area has been that it has the potential to address each and every one of these in some way. We can argue about the extent to which it does it, the efficacy to which it does it, but it has the potential to be able to address each and every one of these in a single step, even including some of the things here related to white blood cells that we haven't talked about at all today in this context.

We have to balance that against the precariousness of decision-making, and there are some real concerns that have to be addressed. The potential to decrease product efficacy, to increase adverse events that may be associated with the changed products, to decrease product availability, to introduce new risks due to blood product alteration, toxicities due to new chemical entities in the blood supply, or new sources of processing errors.

And I think importantly we cannot eliminate the human factor here, the potential that any decision will be criticized as being at fault and wrong, often regardless of the facts. The teeter-totter analogy is a very good
one to me, because it takes at least two people. Playing on a seesaw by yourself isn't very much fun. You have to sit on opposite sides.

If you both sit on the same side, it doesn't make a lot of sense. Usually you have to face each other in opposition. There has to be an element of trust involved, because you're going up or down at different times. And the worst thing that can happen to you is that while you're up, the other person decides to jump off.

And so I think that it's a good analogy for the factors that have to be considered in some of the decision-making processes here. What are suggestions that I would have, because the organizers asked for some suggestions. And I don't like to just identify problems, but also like to talk about potential solutions or suggestions.

I think one of the things that need to be factored in here is to consider where and when it makes sense to apply pathogen-reduction in combination with or in lieu of testing or deferrals. Be clear on what is needed to address concerns with PRT and move forward in a realistic way that factors in the economics of blood and
the realization that no decision can ever be without risk.

If there is one principle of risk analysis, that's true. There's no decision that's without risk, no matter how we analyze it. Don't propagate the illusion that one method will solve all the problems, that it can be perfect, or that it needs to be perfect in order to be considered relevant. We would never do anything if that were the case.

Factor in the future. We either have to be prepared to act or prepared to react. And unfortunately, failure is an option. It may not be a very satisfying one, but it can happen. And finally, understand that we can only collectively fail or collectively succeed in this process. I do believe that it has to be a collaboration among many different groups in order to make this happen.

And I think finally we have to realize that what hangs in the balance is really our collective future. Thank you very much.

(Applause)

DR. ALTER: Wonderful speech, Ray, really provocative. Questions for Dr. Goodrich?

(No response.)
DR. ALTER: No questions. Okay, you were so lucid that there's no need.

(Laughter)

SPEAKER: Well, while we are trying to get the Apple user set up here, let me just comment about Dr. Goodrich's presentation. I think the analogy with the teetertotter is very appropriate, and I think that many times with both the public sector and the private sector, we really need to remember that analogy that we have to face each other and we have to be able to balance the act. And I think that you've given us a lot of food for thought to move forward.

And I think this is the one of the problems that we've had over the years is that just how do we move forward. But clearly with some of the agents that have been identified this morning, as you said, you know, there are some countries that probably are not addressing the same challenges as we are at the present time because they have already migrated to pathogen reduction. But as you said, there's still a lot more to be done. So thank you very much.

Our next speaker today is Dr. Clark Tibbetts. He
is the executive vice president and chief technology
officer and chair of the board of TessArae, a company that
he founded in 2005. Clark trained in chemistry and
biophysics, followed by post-doctorate in molecular
virology research in Wallenberg Laboratory at the
University Uppsala in Sweden.

And during the Human Genome Project, he was
engaged in funded research and as multiple-term member of
the national genomic research review committee overseeing
research progress in genome mapping and sequencing at the
NIH funded centers. It's an honor to have Dr. Tibbetts
with us, and he will be giving us a presentation on High
Multiplicity Resequencing Pathogen Microarray for Emerging
Infectious Diseases.

HIGH MULTIPLICITY RESEQUENCING PATHOGEN MICROARRAYS (RPM)
FOR EMERGING INFECTIOUS DISEASES

MR. TIBBETTS: So can everybody hear me in back,
terrific. Thank you, Harvey and Jerry, and thank you, Dr.
Atreya and Dr. Nakhasi for making it possible for me to
come into your community, and certainly begin a process of
learning a lot of things. I'd also like to acknowledge right at the outset, a terrific team that I had the privilege to work with from 2002 to 2005 within the Department of Defense, representing the multiple services and about 75 physicians, scientists, engineers, nurses, military training specialists, line officers, line enlisted personnel, as well as some of the DOE national laboratories and joint Department of Defense facilities.

We had a concept in 2001, of needing technology that could address infectious diseases in a day-to-day way become almost indispensable for the practice of infectious disease medicine. And at the same time, for free, screen for any possible emergent natural or hostile biothreat that might come up in any particular encounter with the patient, sort of looking for the zebra in the stampede of horses.

It was a great team. Many of us were still working together in different ways through cooperative research and development agreements. But the technology belongs to the government. TessArae is a licensee of the government to commercialize that technology, and as an owner of the company, I make no representations other than what I say today is my own opinion and probably goes for
the company as well.

So we've seen from earlier presentations today, attempts to prioritize emerging infectious disease threats according to various perspectives, whether it's the public awareness and alarm over a potential or perceived threat, or whether there is good hard science of pathology and epidemiology to back up the potential threat. And in this case, I've just put down the lists of viruses of prokaryotic bacteria and eukaryotic parasites pathogens, and colored them by the priority levels that they've been given.

I don't make any assertion that these are absolutely correct or up to date. This was made a few months ago. But what I want to point out is that as a decision support tool, and almost all of the talks so far today have been talking about making tough decisions with insufficient information.

As a decision support tool, this technology I'm going to describe today can very easily, in a single aliquot of a single specimen within a single day, give you a very accurate description of any or all of these different pathogens that could affect blood or blood
products or tissues or organs for donation with sensitivity that is unmatched -- well, it's not superseded by any other technology. And for the first time, a diagnostic technology that breaks the receiver-operator curve, because it simultaneously optimizes specificity of the detected entities identification as well as sensitivity to detect it. And it's really a remarkable technology.

But it does go in the phase of conventional approaches to diagnostics that more often than not test one thing at a time, and uses a surrogate biomarker to carry out that test where a measurement of the signal from the biomarker is translated by inference to presence or absence of a detected target pathogen.

And the only barriers to putting such a test in your hands -- they're not economic and they're not technical; they're regulatory. This is so different than conventional diagnostic technologies that are used. Because they are available by public health authorities to make screening and surveillance decisions that the regulatory barriers that are imposed on those diagnostic tools actually preclude this kind of technology being offered by vendors to the community that needs this.
technology until this technology that I'm going to talk about today actually comes up.

And -- yeah, thank you. I'll get to the hoarseness here in a minute. I don't want to take anything away from Dr. Hughes' suggestion that balamuthia mandrillaris is a very exotic potential threat to the blood supply that only his presentation has. So I slip this slide back in. The New York Times article on the left actually appeared the morning that we went over to talk with Dr. Holmberg in his office about this technology for the first time. And four patients received transplants from a Mississippi organ donor that apparently had been infected by this, not actually that rare freshwater amoeboid parasite.

But what's rare is, if you get the always terminal encephalitis resulting from that infection if you happened to be immunocompromised. And what this test can do, that I'm describing, is not only the list that I showed in the previous slide, but in very, very short order, at practically no additional cost, can iterate an update, and put in organism like this on regardless of what it's prevalence might be in the donor supply because the
consequences of a failed detection could be catastrophic for a particular individual.

There is not a cost issue for addressing rare prevalence emerging pathogens of concern. And in fact, it would be very, very easy on that same small assay to include not only balamuthia, but related amoeboid pathogens, Acanthamoeba and Naegleria. And one of the things I learned in looking into this is that acanthamoeba happens to be a very strong carrier of the MRSA Staph aureus methicillin-resistant strains.

It can carry thousands and thousands and thousands of these bacteria within each amoeboid cell. And if you get infected by swimming in a local swimming hall, it's very more likely that you will get ill from the MRSA than you will from the balamuthia. So how does this technology work?

I said we eschew the idea of using conventionally designed biomarkers, indirect indicators of presence or absence of the particular target. And we go backwards to the legacies of the Human Genome Project that gave us better, faster, cheaper instruments to sequence genes and a massive legacy database continuing to expand, of genes that
represent all sorts of organisms of concern in infectious
diseases. So in this particular case, we have a gene, the
hemagglutinin H5 from avian H5N1 highly pathogenic strain.

That's our detector. And the assay on this glass
chip actually sequences this gene if and only if there are
templates in the specimen from which it can be sequenced.
And it simultaneously sequences about two other -- 200
other genes on the same chip in the same assay of the same
specimen. So what we get from this is if we can read this
sequence, we are not longer inferring that that specimen
has H5 in it. This is what you see, what you got
diagnostics.

And not only that, when you see it, you can see
this particular locus which is the hemagglutinin cleavage
site, and the codons there for arginines and lysines will
give away that this is a highly pathogenic string of H5N1.
And similarly here, you could be somewhat appeased by the
fact that these three codons are part of the hemagglutinin
receptor binding site for infecting cells, and these three
particular codons make it very, very good at binding to
chicken gut receptors as opposed to human respiratory track
receptors.
Now, if you do a PCR test, it's very, very sensitive and relatively fast and not very expensive, but the information you get from a single test tells you nothing whatsoever about the sequence that's used to make the biomarker test work. It's this area down in the carboxy-coding terminal region of the hemagglutinin. And if you measure physically, the amplification of that sequence from the primers, then you conclude H5 is present. But you don't know if it's HP or LP, you don't know if it binds through receptors or not, and since the only test for one gene, you don't know if it's H5N1 or H5N2 or H5N3.

And in fact, there are risks that even though this may work and amplify, it may amplify something from a different hemagglutinin subtype. That's a problem. Or it may fail to recognize a perfectly fine H5 that's mutated at one of the critical primer binding or probe sites and give you false negative. It's very hard to imagine how a test that relies on sequencing the gene, if and only -- if the template is present in the sample can give you a false positive if it gives you a nice, nearly full length sequence of the gene, and maybe two or three other genes for that particular target.
Now, how does it work? It's the DNA sequencing instrument. If we imagine this is the target gene sequence, and at this particular locus, a CG-base pair, the assay mechanism has four nearly identical oligonucler type probes, about the same size as PCR primers and probes. And they are nearly identical except at the middle base; 13 out of 25, they can either be A, C, G or T. And only one of them will perfectly match the target.

So whichever one matches best is most likely, perfectly complimentary to the target and tells you on that strand, if the G matches to the C, that there is a C at that locus. And you have four other oligonuclear types of this strand, probing to see if it's a gene.

And if they agree, you're pretty sure you have a CG at that site. You've sequenced one nuclear type. Not a lot of information. So we get eight more nuclear types to probe essentially sequence positions 2 to 26. And again, it's a CG next to the preceding CG. And then positions 3 to 27, 8 more probes, and you read in this case, the 8 oligocenter matches the T and the T matches the A. And you do this for hundreds of thousands or millions of these probes in every single assay.
And it's cheap. And it works. It has extremely high coverage. The accuracy for calling (phonetic) basis is at least as good as the Bermuda standard of finished genome sequencing. So here is how the application works for a model of respiratory diseases, some of which are on the lists of potentially emerging threats to the blood supply that's more topical. So please don't get lost in the fact that this is a respiratory disease panel.

It was designed in 2006 and 2007, and it was designed at the time where avian H5N1 was emergent and considered to be a major risk. But instead of the traditional diagnostic approach to develop a probe for N hemagglutinin gene of H5, this looks at all possible flavors of hemagglutinin subtypes, and all possible flavors of neuromyelitis subtypes in order to accurately and directly determine by sequencing what is the subtype of one or more viruses that maybe present in this specimen.

And we also have influenza type B. Now interesting, there is a lot of room left over after sequencing all of those genes like I just showed you earlier. And so we put down a lot of viruses that in the middle of flu season, may actually be the etiology of an
acute respiratory infection with no flu whatsoever. Or as we have found out, because we assay for all these things simultaneously, they can co-infect with influenza and aggravate the morbidity of the infection and perhaps warrant a little more attentive care than go home, don't go to work, don't go to school, take aspirin, rest, whatever.

And so you hear a little bit of hoarseness. I happen to know that three weeks ago on Monday, I did a throat swarm and the convalescence you are hearing is parainfluenza virus type 3, okay. There are lots of other stories like that. Now, in addition to other viruses that can cause respiratory infections, bacteria can cause respiratory infection. And in fact, some of these bacteria can cause symptoms that can be misdiagnosed as flu.

You know, they say diagnostic testing maybe why bother, flip a coin, you're just as likely to be right as to whether you should or shouldn't use an antibiotic with someone who comes in with flu symptoms during flu season. On the other hand, a lot of these agents which can go on to cause secondary respiratory infections and pneumonia actually co-infect with flu very frequently.

And in fact, if you go back in history to the big
The 1918 flu pandemic, the majority of deaths from that are thought to have been secondary bacterial pneumonia, not primary infection from the flu itself. And that's also an argument that's been raised even with the most recent 2009 H1N1; it's not necessarily a consensus on that position yet, but I know that in countries like Mexico they are convinced that secondary bacterial pneumonia was the primary culprit in the elevated mortality associated with the early stage of the outbreak.

So this assay has almost a million probes on a glass chip the size of your thumb. It can read 117,000 base pairs, a pretty much real estate model, zero sum, got to take somebody off the block if you want to put a different target in. But that's a lot of sequencing in one aliquot of one specimen in a single day assay.

Now, I want to show you how well it works. These are type A flu virus components in the 2004-2005 configuration of flu vaccine. And you won't have to remember all of these strains, but I'll just mention them once. New Caledonia/20/1999 was the H1N1 target and in -- on the chip, we have the Canterbury 125 H3N2 as a detector. So the H1N1 is the same as in the vaccine being used a
detector. The H3N2 is not the same as in the vaccine.

And so let's see what happened with the vaccine. This is the scan of the chip and this is all of the real estate dedicated to all of those influenza virus genes that I showed you. All of this is down here, Bordetella, strep A, adenovirus, mycoplasma whatever.

There's almost nothing down here except short probes that light up and could be measured signals as if they were PCR probes or primers. But in this assay, we don't measure biomarkers, we don't care. We look for information. And in this area, where there is a lot of flu, we can see that there is a lot of information and we look at the signals from our probes in the context to one another.

Four probes for each base on opposite strands and then overlapping with each other, 96 percent sequence identical, 2 to 26, 3 to 27, 4 to 28, or 115 to whatever 115 plus 25 is.

If we take just a short segment of this information-rich area from the flu real estate section, we can see that it's nicely organized. And if I put on the crib sheet, you can see it's organized in squares.
Remember the four oligo probes to interrogate each base on each complimentary strand. Well, this is a stretch of reading one complimentary strand. We can read a T in the upper left and then 2Gs in the lower left and then 4 As in the row in the lower right, gets boring pretty quickly. Here are 45 bases read off directly. You see it.

There's no question that whatever the sequence is, had a template present in the specimen to allow us to determine it and allowed us to determine frankly 1,500 base pairs of that particular gene. We take just this short 45 nucleotides that we read by eye, everybody is an expert now, and we put it to the universe of all sequences, about 12 million sequence records now out there, lots of pathogens, lots of humans, lots of other organisms.

The only thing it matches in the whole universe of sequence space is hemagglutinin 1, about 600 hits out of 12 million. But what's interesting is, if you put the whole 1,500 basis that the assay reads against the same database, you get six hits. And all six hits are New Caledonia/20/1999; that strain and no other of any other flu strain that's even been sequenced.

Now, let's look a little bit at some of the
sequences. You don't have to read any of this. But these are the sequences that were read off the chip against the most similar sequence found in the universe of sequences in the GenBank or a validated reference database that we have like GenBank. If we look at the matrix gene of this vaccine prep that we just were looking at, the matrix gene detector tile on a chip is Canterbury/100/2000.

But the sequence is best matched in the universe of all spaces by a 76-year-old matrix gene from the Puerto Rico/8/1934 strain of H1N1. Seventy-six years earlier, the detector picks it up and tells you it's that and nothing else. And the same thing that's interesting is we have a matrix gene detector that comes from a seasonal H3N2 on the chip and it translates to exactly the same sequence.

And that happens to be the master donor strain that's used by all of the makers of inactivated flu virus vaccines to be the internal genes other than the specific H and the specific N. The methodology lets you determine the strain and the variant, going back 76 years, it works perfectly. But it also lets you look into the future. Let's stop for a second. How many PCR assays have ever been designed and delivered without any a priori
information at all about the sequences of the target that
they would need to identify, zero.

You can't design an assay, and one of the worst
things about that constraint is you have to design an assay
that matches that strain and only that if it's going to be
useful as a diagnostic test. Well, this was designed in
2006-2007, before the 2009-'10 vaccines were configured
with 2007 strain a South Dakota N1 -- H1N1.

And we got a perfect match of every base that we
read off of the chip matches the South Dakota strain 6/2007
precisely over the full 1,200 basis that we read for the
neuraminidase. This is the just the carboxy-terminal
coding half of the neuraminidase. And just like with the
hemagglutinin -- and I showed you earlier what's nice is
that this lets you take, here's what you read off of the
chip and at codon position 274, we have CAT, that's a
histidine codon.

That's very reassuring. It means that they gave
the vaccine this year that was not representing a tamiflu
resistance strain. This is one of the culprit loci, if
that changes to a TAT, it's a tyrosine codon, and it's a
signature marker for oseltamivir resistance. We can read
that, it comes off of the assay. It's not a green light that says we've got flu, and maybe it's right, maybe it's wrong. It is what it is.

And interesting, this is flu mist. The matrix gene and the NS gene and the PB2 genes and all the other genes don't match this 76-year-old Puerto Rico strain as a master donor virus because MedImmune uses a cold adapted Ann Arbor/6/1968 H2N2 as their master donor virus strain. And that's what it reads, and nothing else.

Now, I'm going to take you quickly through the performance. This was an assay we did as part of getting approval from the FDA OIVD to use under emergency use authorization for detecting the outbreak flu relative to the seasonal flu strains. These are the triplicate assays looking for positive and negatives, a 100 percent positive until you reach a dilution endpoint at which it collapses and then at the end point, you do a 20-fold replicate to show that the LoD is accurately determined.

And that's exactly what you get. And in fact, it superimposes on what the CDC assay gets for its H1 analytes in the PCR assay. And so the assay that we are showing you that gives you a sequence instead of a green light signal
has the same sensitivity as the best of the PCR assays that are out there, it takes the advantage of amplification to get that sensitivity.

This is a measure of the amount of DNA sequence that can be read off of the detectors. And what's nice is that while this quantile limit of dilution series, behaves as expected, the amount of sequence that you can read from the detector tile is logged linear with dilution, and allows it to be semi-quantitative estimate of viral load in the original specimen.

The limit of detection for this assay or the best of any PCR assays is on the order of about 10 virus particles to 31 virus particles per tested aliquot. And we get the same limits of dilution as with other molecular tests. The only difference is we're testing for 200 different genes simultaneously, as opposed to one probe for one gene.

Specificity, we talked about that in terms of the vaccine strains. The USDA Southeast Poultry Research Lab sent us a box of frozen specimens from the national repository of avian flu strains. And our deal was we'd open the box one morning and we'd send them a table like
this that evening with all the results.

I got a call from David Swain (phonetic) at 10:00 o'clock that night say, Clark, we've got to open up and unblind this data and talk about it tomorrow morning. I said, fine, what time. Well, the reason he was excited was every one of these strains, from mundane H1N1 to pretty exotic H15N5 or H15N9, everyone was spot on. This is the first time anybody had done a test on a single day across the full spectrum of what they have sent blind and we got the subtypes all right.

You know, there is a lot more diversity among type A flu found from avians that there is from typical human infections. But it was worse than that because in blue here, from the sequences that we determined from H and N, we told them what the reference strain was that they had sent us blind. And it was spot on, five exceptions in white. David said, don't worry about it. We haven't submitted those to any genome database yet, but we compared them; the sequences you told us were most similar had mismatches, but the real sequences don't.

Okay, so it's a sequencing method, and even these two yellow, those were the spoofs. This is avian
metapneumovirus, no flu detected, and we read from the avian metapneumovirus tiles that are on the chip and translated to the most similar sequence that was type C avian metapneumovirus Colorado strain, which was exactly what they sent us blind.

This is an avian paramyxovirus virus type I or Newcastle disease virus. We didn't have anything similar enough on the human respiratory agent chip to pick up Newcastle disease. But we had another chip designed to look at veterinary and type a, b, c biothreat agents. Newcastles was on there; we did it, and although that was not blind, we came up correctly and identified it as a velogenic strain from the California outbreaks. They were pretty surprised.

Okay, we have a study going on involving 12 different hospitals looking at pediatric bronchiolitis. And the take-home message from this slide is multiplicity. Most clinical situations looking at bronchiolitis assume RSV. We'll do a PCR test to confirm it. The PCR tests typically have a false negative rate, or no-report rate of about 25 to 30 percent.

They typically treat as if it were RSV, even if
the result comes back negative. We tested 133 of these samples, compared it to the PCR tests and all of that was favorable. We got 65 percent that were RSV positive and we could differentiate them between type A and B. They say we don't care. But what's interesting is we found all of these other viruses co-infecting only with RSV type A, but not type B.

Maybe it makes a difference to know if it's RSV A or B, because maybe the patients with RSV A need a little more watchfulness. They might have metapneumovirus or adenovirus or coronavirus. You might want to know that, you might want to see these things.

And in addition, we found overt respiratory pathogens of a bacterial nature in these same specimens that were RSV positive, including one mercer strain of staph, and one strain that was RSV negative had Pseudomonas with a very, very high load of exotoxin gene. So we think that patient should have been recognized on admission and treated maybe a little differently than the assumption of RSV bronchiolitis.

In late April of 2009, we had effectively five sentinel cases tested with this technology. I can tell you
about two of them. The other three were not ours -- proprietary to talk about, but they will come out in publications. This is an example of what happened. In late April, we submitted the sequences of detected genes from a patient who'd come back from Mexico, had a mild flu, read about the outbreak, got worried, got tested. And pretty much the same story for the other four cases.

And in this particular case, we found that they had a matrix gene that looked like a highly pathogenic H5N1. Okay, four different strains were most similar. It didn't match. There were lots of mismatches between what we read and what the sequences did, but different than a PCR test. We weren't stopped. We didn't have a 72 percent of scale green light measurement that we could analyze at a later time when we had more information, we had sequence.

So a week later, first the GIASAID European -- German-Swiss database published the first sequences from the outbreak strain. And about a week later, GenBank picked those sequences up. As soon as the database was updated, we went from imperfect matches to very odd sentinel event flags to, hey guys, perfect match to all of the outbreak strain.
And all of the dozens of samples we analyzed since in working through with the FDA to get our emergency use authorization had essentially the same results. They are perfect matches to the outbreak strain and not to anything else. And that's interesting again because this assay was developed 3 years before the outbreak. It sees into the future. It's probably the only kind of technology for diagnostics that is prospective.

We heard one of the earlier speakers talking about the need to be preemptive. This is a tool that could help be prospective and detect and identify and characterize emerging strains of any number of different pathogens that maybe relevant to a particular specimen.

And we were pleased because our colleagues in China published on the same day as in the U.S. the granting of the emergency use authorization. This is the first infectious disease diagnostic test that's highly multiplexed and uses DNA sequencing as the foundation of the test. It's just as sensitive as a PCR test, far more specific than a PCR test, not costing much more.

Certainly costs a lot less to do this one test than it does to do 30 PCR tests for the different types of
viruses and bacteria that are in there, and a higher sensitivity because you don't have to divide your sample into aliquot; it's just all one aliquot.

So let's think about prospective diagnostics. This is when the test I'd been describing was validated in a large-scale retrospective infectious respiratory disease program at the Naval Health Research Center in October, November, December of '07. And then this outbreak appeared first with reports of deaths in Mexico, and it was only after sequences were available, but not yet deposited it into public databases that the CDC could develop a PCR assay leveraging its previous PCR assays for H1 and H3 and H5 to specifically recognize the flu strain of 2009 H1N1.

And the only problem with that assay is it can only recognize that original strain. It cannot tell when variants arise, other than by failure of the test. For example, if it were to re-assort with seasonal H1N1 and swap hemagglutinins, the testing protocol would determine that it's seasonal H1, and they would never do the swine flu test. And you can imagine all sorts of other Franken-Virus scenarios that I think frankly are likely to be the next emergent step in this pandemic strain.
And we're talking about this technology for emerging infectious diseases, what better place to put it than in the middle of Central Africa, in IMBO, on former grounds of Njala University, on a hospital compound. The locals built a clinical laboratory, satellite-linked to TessArae and the Naval Research Laboratory here in Washington.

It's solar-powered. All of the samples they're collecting for endemic and epidemic outbreaks of Lassa fever are geolocated by GPS. This is one of the two interns we trained. They are now training the next generation of local technicians to actually operate the machinery. They've been trained by Alphametrics for all of the engineering and maintenance they can do onsite, and it's up and running.

One of the individuals who was testing the flu chip I just described had an infected finger. And I thought, swap, assay, mercer together with the Panton-Valentine necrotizing pneumonia factor.

And just to end the presentation, we are working with the FDA. I mentioned already that we've had a great cooperative relationship with CDRH OIVD for getting this
technology reviewed and evaluated. We've just started a recent relationship with CBER to look at some blood-borne pathogen chips like I projected at the first slide. And we recently finished a USDA-funded SBIR grant for a food-borne pathogen chip, and this is essentially the same size and mechanics as what we're proposing as a blood-borne pathogen chip.

But we have the leftover arrays from the phase I SBIR. We took them over to Laurel, to the Center for Food Safety and Nutrition of the FDA, and they're delighted to begin the secondary validation process as a collaborative, no-cost CRADA-like engagement. And so with that, I will stop, and say thank you for your attention, and also thank you for everything I've been able to listen and learn from.

(Applause)

Q & A

SPEAKER: We have time for just one question if there is a question.

MR. HARVEY: I have.

SPEAKER: Okay.
MR. HARVEY: (Off mike) -- question. I wasn't clear upfront what goes on to the -- what do you do with the sample? Does it have to be amplified?

MR. TIBBETTS: Take your specimen.

MR. HARVEY: Yeah.

MR. TIBBETTS: Take your specimen, you do a total nucleic acid extraction by the simplest techniques that are as old as I am, and then you do a reverse transcriptase to get cDNA copies of any RNA from viral genomes, and then you put them all into a highly multiplexed amplification that's extremely relaxed. It would never work for any PCR test. It'd be littered with false positives and primer dimers and everything. But what makes this thing magic is that it totally separates amplification to achieve high sensitivity from detection.

In PCR test, you measure the accumulation of amplicons. In this test, it's only those amplicons whose sequences can be transduced by hybridization to the probe array on the chip. And if you think about multiplex PCR assay something like Luminex offers with RVP, it's a great assay, but you are limited in time to physically separate the multiple PCR products before you can individually
measure them.

That hybridization's physical separation step is exactly what takes place on the microarray except that we're separating out sequences that combine and compete to bind to about a million different probes simultaneously; from which in context to one another, we can read sequences.

MR. HARVEY: Thank you.

SPEAKER: Mike Strong?

MR. STRONG: I'm a little disappointed. I thought Harvey was going to ask you if Lady Gaga worked in your lab. But my question was a technical one similar to Harvey's, which is -- along with the technical approach to it; the sample volume, and the throughput time?

MR. TIBBETTS: All right. If you are running in a high throughput environment, say 50 to 100 samples a day, the logistics in operation for throughput are exactly the same as running multiplex PCR. You get your results late the same day if you start early in the morning, or you get them first thing the next morning.

The overall assay for single specimens from receipt of the sample to sending out the e-mail or posting
the secure web portal results for the end user, is as little as 8 hours and usually closer to 10 if you really push it. But it's very easy-to-batch process, and once you get into that queue, it's really no different in terms of throughput. The instrumentation systems are available to run hundreds of these samples a day with no problem at all in one laboratory. Did that get the question and answer? Okay. I think -- (off mike) -- enjoyed.

MR. STRONG: Okay, thank you.

MR. TIBBETTS: Thank you both very much. Thank you everyone.

(Applause)

REDUCING THE RISK OF TRANSMITTING SPONGIFORM ENCEPHALOPATHIES BY HUMAN BLOOD AND BLOOD PRODUCTS

DR. ALTER: It has been a fascinating session, thank you, Clark. Our last speaker in this session is David Asher. David is a graduate of Harvard College and Harvard Medical School. He has been with the FDA since 1995, but prior to that time, he spent 25 years with the - - in the Laboratory of Central Nervous System Studies at
So he was involved in the very early spongiform encephalopathy, the kuru study, the novel prize-winning study of Gajdusek, and thereafter long before prions were known to be prions. So he has a huge experience. He is one of the leading people in the whole prion field throughout the world. And he will update us on the currents of variant CJD and the ways we might now prevent it, if any.

DR. ASHER: Thank you, Harvey, and thanks to the organizers for inviting me. As usual, I have too many slides, but in the hour it grows late, but many of the points that I was going to make have been very well made by previous speakers. And some of the material I provide is just for reference so we can skip through those.

Spongiform encephalopathy is example of a low probability but with very high consequence infection, always fatal. Take a brain that should look like this, and turn it into something like that or even like that, just terrible, terrible disease.

First, I want to make sure that I acknowledge everybody who lent me slides, particularly Luisa Gregori
who is a real TSE blood specialist in our laboratory, unable to be here because of a family illness; Pedro Piccardo, who is in neuropathologist and an expert in prion proteins; Kitty Pomeroy who helps us with just about everything; Mahmood Farshid, who is our CBER expert on validation of pathogen removal procedures from blood products; Dorothy Scott in plasma derivatives; Steve Anderson and Hong Yam in our Office of Biostatistics and Epidemiology for Risk Assessment.

I will begin by talking briefly about -- it seems to have deformatted on this computer, forgive it, about the TSE agents called prions, their -- the detection of infection, prion protein and infectivity, bovine spongiform encephalopathy recent trends, variant Creutzfeldt-Jakob disease briefly, our overall responses to the outbreaks of BSE and variant Creutzfeldt-Jakob disease particularly one new and one proposed rule, not involving blood products directly. And then I have progenic TSEs maintaining the safety of medical products with special attention to blood components and plasma, plasma derivatives.

Except in passing, I won't mention Kuru,
although I will say that it is an informative example in that it shows that if you can prevent exposure to a TSE agent, you can eliminate the disease. So not all is not lost. Creutzfeldt-Jakob disease, I'll speak mainly about variant Creutzfeldt-Jakob disease just briefly about other forms of Creutzfeldt-Jakob disease.

Of the several animal TSEs, I will speak only about BSE, because it is the one known zoonotic animal TSE that cause variant Creutzfeldt-Jakob disease although I will say that knowing that BSE emerged from the universe of scrapie strains, or at least that's most likely the source of it, and knowing how quickly chronic wasting disease is spreading throughout the United States, even though it has not been recognized to cause disease in human beings, but because all these animal diseases are experimentally transmissible to monkeys, it seems only prudent that whenever possible, we avoid exposure to the animal TSE agents.

First, a word about the prion protein. This was first seen in brains of patients with kuru where it formed these amorphous so-called amyloid plaques. And the -- perhaps 20 years later, the protein was visualized by Pat
Merz at Staten Island by electron microscopy. She called it scrapie-associated filament. It was more fully characterized by Stan Prusiner who named it the prion protein.

The protein is a misfolded derivative of a normal cell, ubiquitous normal cellular protein. The normal protein is mainly alpha-helical. In confirmation, the abnormal protein has a high β-sheet content, and I should point out that its true structure is not known, their hypothetical structure is, but it doesn't crystallize and it has not been possible to -- thus far to determine its accurate tertiary structure.

The protein is made out of approximately 250 amino acids. There is a variable region of -- duplicate of octo-peptide repeats and so the length varies a little bit. There are a number of polymorphisms. The most -- best known of which, there are single nuclear type changes that result in mutations that associate with familial Creutzfeldt-Jakob disease and a variant of it. And perhaps the most interesting polymorphism is in amino acid codon 129, where homozygosity for methionine is highly correlated with increased susceptibility to infection.
That's true of conventional Creutzfeldt-Jakob disease and it's been especially true with variant Creutzfeldt-Jakob disease. Until recently, every clinical case of variant Creutzfeldt-Jakob disease has been, in a person, homozygous for methionine at that locus. So, well last year for the first time, a patient heterozygous at that locus was described and a number of inapparent presumably pre-clinical infections have been recognized in people who are homozygous for valine or heterozygous at that locus.

To repeat, the abnormal protein is the abnormally folded product of a normal cellular protein. It's relatively insoluble -- since the abnormal form is relatively insoluble in detergent salt solution, relatively resistant to digestion with the proteolytic enzyme proteinase K and those two features have been used to define it.

I have mentioned the familial CJD associated with inserted duplications, point mutations and possibly with a dilution. Although the function of the prion protein, the normal function is not known, it's clear that it's some sort of luxury protein and that mice and cows
without the protein are normal, but that the protein must be expressed for an animal to be infected with a TSE agent.

It has been proposed by Stanley Prusiner originally to be a self-replicating agent that sometimes misfolded spontaneously. That remains controversial, although it is the most widely accepted hypothesis. The nomenclature is confusing. There are at least five different names being used for the abnormal protein, the first was PrPSc scrapie type. The WHO suggested, in 2005, calling all the abnormal forms PrPTSE, which is what I will do it today.

The agent has some virus-like properties, but it has a constellation of unique properties particularly its inactivation, its resistance to most inactivation procedures, and the lack of any detectable protective immune response. There have been concerns about the protein theory for TSE agents or a number of failures to correlate infectivity with the appearance of prion protein. There is infectivity in tissues without detectable, abnormal prion protein and a number of the proofs asserted showing that there were no nucleic acids
later failed although there are a couple of relatively convincing, more recent proofs, none of them has been independently confirmed.

And those of us who are old enough to remember the 19th century can -- I used to go to the movies with somebody who was born in 1876. So that has to -- at any rate, we can remember that there were spontaneous generation theories for malaria, cholera, and tuberculosis, none of which ultimately proved to be particularly useful.

But the prion hypothesis remains the default theory for the TSE agents. That is the most popular theory considered true until proven false beyond reasonable doubt, and it's the answer that you should give if you have to take an examination in infectious diseases. It is also fair to point out that sometimes default theories turn out to be correct or at least useful. And certainly the association between the prion protein infectivity is sufficiently consistent that it is a useful association and one would have to be a brave person indeed to say that something was safe, if it contained detectable, abnormal prion protein.
This is just an example from Pedro Piccardo to show accumulations of abnormal prion protein in the brains of a mouse. And these mice do not show other signs of spongiform encephalopathy, are perfectly healthy looking, and have normal life spans. It is not this that we are afraid of when we attempt to keep the infectious agents out of biological products.

The leading, remaining proponent of an alternative theory is probably Laura Manuelidis, who has studied tubulovesicular particles that are seen in TSE infected brain tissues and cell cultures. However, no unique nucleic acid has been attributed to these particles.

So the most practical method used to identify potentially infected materials has been the detection of salt, detergent, insoluble, PK resistant prion protein as shown here. In normal, if you detect some prion protein, but when you incubate with proteinase K, it's completely digested. In scrapie infected brains, there is even more programmed prion protein detected. And it remains after digestion with proteinase K. But because of the discrepancies and the lack of sensitivity, most prion
protein assays don't detect protein until you have at least say ten of the fourth 10,000 infectious doses per aliquot tested. So that in the regulatory community, we still rely on infectivity assays.

These were originally done for human agents and nonhuman primates. They are now most often done in a variety of rodents, particularly transgenic rodents expressing the prion proteins of other species.

Now let me just review quickly the status of bovine spongiform encephalopathy which has been the first of the animal diseases, clearly transmissible to human beings. The first case was diagnosed in 1986. Presumably animals were infected probably five or six years earlier. Feed ban, the first of several feed bans was imposed in the United Kingdom in 1990.

In 1988, the disease peaked among cattle. There were something over 37,000 cases a year in the U.K., in 1992 declined thereafter. Last year in the U.K. only 12 cases were seen.

There are 24 other countries that have had BSE, world total more than 187,000 cases diagnosed, reports there must have been many more that were not diagnosed.
We have had in the United States three cases. One came in from Canada, diagnosed in 2003, one in 2006, and one in 2007. Canada has now had 18 recognized cases. So far as I know, all of those cases in Canada in the western part of the country.

There are only six cases that have high prevalence of BSE. And I -- but a number of other cases, there's -- and other countries, they are still seeing cases. Twelve countries have reported no cases since 2008 including the United States. But, unfortunately, last year there were 14 countries, and two have subsequently fallen off the list, Denmark and the Czech Republic. The point is that this disease is still around, and it's not clear when it will finally be eradicated.

In addition, the United Kingdom shows widespread exports of meat and bone meal, the presumed vector of this infection, sold all over the world including the United States. But large amounts where sold into the former Soviet Union and the Southeast Asia. They have reported no cases, but we wonder if their surveillance systems are very robust. And in any case, we must still consider this potentially a worldwide infection of cattle, fortunately
coming under control in Western Europe and we hope in North America as well.

The World Organization for Animal Health, the OIE, has started to a system of BSE risk categorization. Two categories of interest, one negligible BSE risk, and the other controlled BSE risk. I won't go through the details of their criteria. There are in the slide; there are 11 negligible risk countries including Australia, New Zealand, some countries of northern Europe and South America; 32 controlled risk countries including the USA.

I must say I am a little uncomfortable categorizing the USA risk together with those of the U.K., Portugal, and Spain. But, so far as I know, the USDA has accepted their classification. It hasn't, not at least publicly, challenged them. The concern with BSE is that it is -- has transmitted disease to human beings, variant CJD, first described in the medical literature in 1996. The first teenager became ill probably in 1994, very different from sporadic CJD in its epidemiology. Much younger kids in their teens have been found with it in mean age 29 years or slightly shorter duration, some differences in clinical presentation and there are
differences in the pathology.

Perhaps 15 percent of patients with Creutzfeldt-Jakob disease have *amyloid plaques*. All the patients with variant CJD have had *amyloid plaques*, often -- sorry always surrounded, at least some of them with these haloes or vacuoles called florid or flower like plaques. And their accumulations in variant CJD of prion protein in lymphoid tissues visible under the light microscope. And no one has to work very hard to find prion protein, never seen by you know, histo-chemistry in sporadic CJD. So it's a different looking disease.

As Sue summarized for you earlier today, there are now, I have got 218 cases of variant CJD, 172 of them in the United Kingdom, 46 outside the United Kingdom. Some of them were clearly acquired in the United Kingdom. We've had three cases in the United States, two of whom were long-time residents of the United Kingdom and one a long-term resident of Saudi Arabia; one case in Canada, also a long-time resident of the United Kingdom.

Deaths in the United Kingdom peaked about eight years after the peak of BSE diagnosed in cattle. One could use that to approximate a possible incubation
period. Sue has already reported to you the four transfusion transmitted cases which were, what, on occasion are our concern in this group. And, as most of you know, in February of last year the United Kingdom reported a case of what appeared to be a pre-clinical infection in an elderly man who was a -- had hemophilia and had been receiving treatments with a plasma derived factor, factor 8.

One of the donors to the factor 8 he received was identified with variant CJD although an epidemiological study in the United Kingdom suggested that at least given some assumptions of prevalence, he might have been equally likely to have been infected from one of the non-implicated batches. Of course, it is not possible to know.

The incubation periods are important because that lets us make some projections about how long someone might be carrying a transmissible agent in blood. To me, one of the most informative cases is a case in Japan, who spent only 24 days in the United Kingdom and three days in France, 12 years before returning Japan. Japan has some small amount of BSE on its own but the most probable
source of his infection was the United Kingdom and it
gives you a 12-year incubation period.

And the few other people who came down after
exposures in the United Kingdom, their exposures were much
longer so it's harder to calculate an incubation period.
But they fall into that approximate range. The
transfusions transmitted cases had somewhat shorter
incubation period, anywhere from 6.3 to 8.5 years and the
plasma derivative associated case, you can't see it on
this projection, but it is 11 years if the implicated
donor was, in fact, the source.

Steve Anderson and Hong Yang have done
distributions of the likely incubation periods of persons
with the methionine homonzygous and other genotypes. And
the disturbing thing is it's certainly possible that there
are going to be long tails to the number of people
incubating variant CJD. And at the end of last year,
Cosky (phonetic) and colleagues described typical variant
CJD in a person heterozygous for methionine and valium at
codon 129. Now we know that people with all genotypes
presumably can be expected to come down with infection.

We hope that the peak will be much smaller in
people with heterozygous genotype who make up about 50 percent of the population in the United Kingdom and probably about the same here. But if it is going to be like sporadic CJD, incubation periods may well exceed 35 years and even 40 years. And those folks are out there and we don't know how many of them are -- will have agent in blood or how long it will last or how much there would be.

I want to mention this because from a public health point of view keeping the cattle herd free of disease is probably the single most important thing that we can do.

And in the context of the United States, the single most important measure taken is to prevent the feeding of contaminated material to a cattle, a feed ban line to affect here removing most mammalian proteins from cattle feed in 1997. And that was expanded in 2008, went into implementation last year to keep the highest risk material, that is brain and spinal cord of animals, over the age of 30 months from rendering for feeding to any kind of farm animals to prevent -- or pet food also to prevent cross-contamination on farms which was a problem
in the United Kingdom.

There won't be time to talk about it, but there has been considerably more trouble with dura mater allograft which has infected over 150 recipients. Corneas have infected a couple of people with Creutzfeldt-Jakob disease and neuro surgical instruments. We have been over the both the blood red blood cells -- by the way, all four of the transfusion transmitted cases were in non-nuclear reduced to red cell concentrates. However, I think the plasma derivative case suggests that that is not going to be enough to remove risk to a safe level.

The general methods for managing risks we have already discussed. Risk can be accepted, reduced by restricting use of product or screening or manufacturing processes. And the FDA is particularly concerned with validating screening tests and validating methods that purport to remove infected material from final products. That's not just blood products; that's all biological products.

In January of 2007, the agency published a proposed medical products rule. I won't go into it except to express my own personal concern about fetal bovine
serum because fetal bovine serum comes from the carcasses of gravid older cows which means that their nervous systems are at greater likelihood, if there is any BSE left in the country, of getting into the product and fetal calf serum is so widely used in vaccines and other biological products.

I have given you a timeline of the history of TSEs and FDA blood safety policies merged. Really the history of really begins in 1978 when Elias and Laura Manuelidis first detected CJD agent in blood of experimentally infected guinea pigs. This was confirmed in 1983 and in the 1983, the FDA issued its first guidance of recommending withdrawal of CJD implicated blood components when a donor had subsequently come down with CJD. I won't go into details, but as most of you know those deferral recommendations were made progressively more stringent over the years.

What do we know about the infection agent in the blood? Almost everything we know we have learned from the work of Bob Rohwer, originally with Paul Brown, later with Luisa Gregori, some work of Paul Brown with Larisa Cervenakova. In experimentally infected hamsters, the

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infectivity is first detectable in blood about 50 percent of the way through incubation period and the amounts detected continued to rise progressively until the animal becomes ill and has to be terminated.

But the amounts are very low. They almost never exceed 10 infectious doses per milliliter which is plenty to infect a recipient, but makes it very difficult to detect because of sampling problems. It makes it very difficult to detect the infectious agent.

In the blood, infectivity can be found in all components. But the components that seem to be intrinsically infected are the nucleated cells and the plasma. Considerable amount of infectivity appears to be intrinsic to the plasma which, of course, contaminates all the other components.

General methods to reducing the risk -- reduce the risk of exposure to the BSE agent through diet and that is what we try to do with the geographic deferrals or other exposures, deferring for use of U.K. bovine insulin, no longer marketed in this country, reduce the risk that the donor was exposed to vCJD of human origin and that means nobody transfused in U.K. after 1980. In 2005-2006,
we proposed modifying that to defer for transfusion in France. There has also been some consideration, at least in the U.K., of deferring people who had risk surgical procedures. We haven't done that.

I won't go through the 2002 deferral guidance which is as most of you know still in force. The proposed modification, we hope, will be finalized this year. It's a striking difference between what's been seen with recipients of implicated transfusions in the United Kingdom and those receiving implicated sporadic CJD transfusions in the United States, described last year by Carrie Dorsey and colleagues from the American Red Cross building on work that was started, I believe, by Marion Sullivan supported by the CDC.

Out of the 26 recipients of labile components of receiving transfusion in the United Kingdom, four of them have already come down with variant CJD whereas 144 recipients have implicated components in the United States. Nobody has been recognized with CJD.

Now the intensity of surveillance is not as good here. A lot of the patients did not get autopsies and some of the recipients received blood collected more than
five before onset. And then so it is not clear that all the donors would have had agent in their blood. But it is reassuring as far as it goes. Is it sufficiently reassuring to change FDA's guidance? It hasn't yet.

Mark Walderhaug showed you this sensitivity analysis performed by Steve Anderson and Hong Yang showing that for plasma derivatives the reduction of infectivity by manufacturing is the single most important factor in reducing the risk. And based on this, the division of hematology has entertained requests or has solicited efforts to validate those steps being used to manufacture various plasma, plasma derivatives and has entertained requests for label claims.

The model for concluding that a method for reducing infectivity is effective was taken from what is done with viruses. For viruses, a process has to -- in order to have a claim has to have at least two effective orthogonal steps to remove or inactivate virus. Each step should drop at least four logs. One of the steps should inactivate the virus. There should be mass balance that you should know where all of the virus that disappeared went, and you should be able to inactivate or remove at
least three logs more than the amount that you think might be present in a worst case.

Of course, we can't do that for spongiform encephalopathies, but we have seen some clearance data presented, first to reiterate that PrPTSE clearance would be acceptable only as a preliminary assessment of probable effectiveness. That is if you do clearance study and you can't get rid of all the abnormal PrPTSE, then you might not want to waste time with that method of removal so that infectivity still required -- demonstration of removal of infectivity still requires bioassays in animals and, of course, it's infectivity that is the actual adverse event of concern.

Our pilot studies with our U.S. licensed plasma-derived factor VIII have all showed substantial clearance of model TSE agents of at least four logs and the product used in the United Kingdom is not licensed in this country. Five products have been granted label claims. Unfortunately, none of those was based on an inactivation step, they were all removal steps of greater concern because, of course, that agent if it is not inactivated, is still available on the filters to infect a subsequent
product if not discarded. And no claim of complete elimination of a TSE agent has been allowed.

It would be very good if we could do Andy Morton test. And you may recall that in 2006 we had a whole session of TSE advisory committee of tests that were in development. The desirable property is that they should be suitable to test individual donations, high throughput, highly analytical sensitivity that is to detect very low concentrations of PrPTSE and all of them that I am aware of are based on -- test and developmental based on the detection of abnormal PRP. They should have reasonable clinical sensitivity. We wouldn't require that every single infected donor be detected. I don't know how you determine that in the first place, but it should be able to eliminate a reasonable number of infected donors from the donor pool.

And it should to have a high specificity that is the inability to discriminate PrPTSE from other proteins yielding a low false-positive rate. And that's a problem. Luisa Gregori summarized at our last TSE meeting all the proteins that are present in human plasma, all of them in great excess to what one would expect for PrPTSE. The
greatest problem is that there is perhaps ten to the fifth more normal PRP circulating in plasma than what you would expect based on the same ratio determined from normal PRP to abnormal PRP in brain, you can predict, what if the ratio stays the same which we don't know, but what it would be in plasma and the PrPTSE would be present in an excess of a hundred thousand fold.

That's important because if you don't get rid of all the normal PRP, or if it is alive and it is supposed to be specific detects even a little bit of the normal PRP, there goes your specificity. And, in fact, nobody has successfully validated one of the tests yet.

Analytical studies, the U.K. has actually a committee that set up an algorithm for what it's going to take to get a test approved in the United Kingdom. There should be convincing analytical studies followed by spiking studies with blinded panels of human plasmas spiked with TSE infected brain tissues. If it does well on that, then with spleen tissue which is supposed to more like blood. Then the test should be able to detect endogenously infected blood from available animal models.

It would be even better if endogenously vCJD
infected nonhuman primate blood could be detected because then exactly the same reagents that are proposed for human use could be used, which of course you can't do with rodents because of the failure of cross-reactivity. And it would nice to have a well characterized human vCJD blood reference material, but not even the U.K. has that.

I won't dwell on it, but there are a number of companies have advertised that they had promising tests and development. We had eight or perhaps it was nine presented in 2006, all except two or three have fallen silent now without bringing a test to market.

Luisa did a web search for the June meeting of last year and found that four other companies were still trying to develop a useful antemortem human blood test. The -- one of the companies, Amorfix, was reporting a specificity study using 10,000 reactive blood donors. Out of 10,000 tested -- six positives out of 10,000 tested in France. It might have been a little reassuring if they used a country that hadn't had 25 cases of variant Creutzfeldt-Jakob disease but that's what they had.

Two of the tests were based on an apparent amplification of abnormal protein. One of them used an
interesting palindromic peptide. They have fallen silent now. The other one, Amprion, is using a very interesting technique called Protein Misfolding Cyclical Amplification. And the basic principle seems to work that as you take a very small amount of abnormal prion protein, abnormal brain tissue, do repeated sonications and the amount of protein increases to a level detectable by Western blot.

To my knowledge, this method has not been subjected to the traditional kind of analysis, comparative analysis side by side with blinded replica, unknown dilutions in plasma or serum compared with other detection methods. The developer of the method is going to be speaking at the FDA on the 26th of May. Perhaps he will have more information to share with us. You are all welcome. Well, not all of you, the room isn't that big. But some of you are welcome there, are welcome to come.

We had mentioned that there is an absence of -- we have given up on human reference materials. They are just not going to be available but Corinne Lasmezas and colleagues have a very interesting model of infection of cynomolgus macaques with variant CJD agent. The infectivity is present in blood and Luisa Gregori is
leading a new effort in the FDA. We finally have approvals and funding and the inoculum and she is going to be infecting cynomolgus macaques and collecting blood at intervals through symptomatic disease.

What we don't have is a well validated sensitive mouse assay because we certainly can't assay for infectivity in other cynomolgus monkeys which would have been the classical way to try to do it. I won't mention this, but she is also working on the use of urine as an alternative test material because in rodents infectivity can be detected in urine. But that's not been done in human urine, but it's very little -- very little investigation has been done with human urine. And in any case, it probably it isn't going to be a suitable donor screening testing in any case.

I share with Sue some sense of enthusiasm for the possibility of blood filters. There are two of them that have been described publicly. We think there may be others in development. The MacoPharma/Prometic: P-Capt Prion Reduction Filter and then the Pall Corporation has a filter. The U.K. Advisory Committee on Safety of Blood, Tissues, and Organs some months ago recommended using a --
one of the filters with leuco reduction to treat blood for recipients in the U.K. under the age of 13.

But the filters are not available in the United States. And of course, here the risk-cost benefit ratio would be quite different from the U.K. because our prevalence is presumably much lower than it is in the U.K.

So to conclude we agree that ante-mortem assays for PrPTSE in blood and tissue donors would be useful. We encourage them; we don't have any available yet. I don't believe that any national authority has approved a test for practical use. There is no proof of concept that PrPTSE is even present in plasma and no test in development to my knowledge has convincingly identified vCJD infected or any other TSE infected human blood. There are some intriguing reports about animals.

There are unresolved issues regarding tests for TSE in blood. There are no TSE blood reference materials, human or nonhuman nor primate blood reference materials available. There has been no confirmatory assay described. And as for other infections of low prevalence, any analytically good but imperfect screening test, any such test would have a very low positive predictive value
which means that most of the positives would be false positives leading to continuing significant donor deferrals and exceptionally difficult donor counseling.

PrP-removal filters have already been recommended in the U.K. but they are not available in the United States. The continued deferral of donors at increased risk for vCJD both food borne and blood borne seems reasonable. It's a low tech approach. It's probably been effective in reducing the risk of transfusion transmitted vCJD here. Of our three vCJD patients identified, two of them -- none of them was a blood donor but had they tried, two of them would have been deferred, the third would not.

It probably causes less emotional distress to be deferred for geographical reason than to get a false positive test result. But the default policy, we acknowledge, is extremely wasteful because it's deferring many otherwise suitable donors. We should probably continue deferring donors transfused in countries with possible high prevalence of preclinical variant CJD, currently the U.K. and France.

But the good news to me is that the need for
donor deferrals and for testing and filtering would --
should decline as more countries implement effective anti-
BSE food and animal feed precautions. And with that, I
close. Sorry, if I ran a little bit over.

(Applause)

Q & A

DR. ALTER: Are there any questions? I think
everybody wants -- Steve?

STEVE: Yeah, I have one quick one. I noticed
from the slides on the actual FDA deferral policies from
the guidance in 2002 that, if I read them correctly, the
exclusion -- deferral criteria for visiting the U.K. are
time limited, 1980 to 1996, but the criteria for visiting
France or the rest of Europe are to the present. And I
wonder if you have thought about reexamining whether to the
present is still indicative given the low rates of vCJD
these days?

DR. ASHER: Yes. We have thought about it. And
I can only speak for myself but we have thought about it a
lot. There are certain problems in Europe. We had a
discussion of food protections in the European Union at the June meeting. And the problem is deciding when which country implemented the same level of food protection that we have considered acceptable in the United Kingdom. But in principle, you are absolutely, you are -- also the cross border exchange in food is greater in continental Europe than it is in spite of the Eurostar Britain is still separated geographically from the rest of -- it's a great train by the way to recommend, but at any rate there are certain difficulties in drawing a bright line between countries.

And I'm -- we didn't get a great deal of assistance from the European Union. Their feeling is they have the directives in place and every country is supposed to be following those directives, and therefore we should assume that they are following those directives and maybe we should. But, in principle, I think that you are absolutely right. When other countries reach the level of food chain protections we have considered acceptable, in the U.K. I can't see any reason for considering that risk to be any greater than that in the U.K. The problem is making the decision country by country.
DR. ALTER: Okay. Well, we are little bit behind. We can all try to get --- (tape interruption.)

SESSION 3: ROUNDTABLE DISCUSSION

MR. NAKHASI: All right, so okay so I think this part of the session is now basically to focus on to the -- having a roundtable discussion, what we learned this morning and this afternoon and where we go from here. I don't think I'm going to leave anybody from here unless we have certain action items before we leave this place.

And I think -- so I think with that in mind, I think, I would like to, you know, the panel members are here, the speakers who talked this morning. And my name is Hira Nakhasi as you've heard by now. You don't know me I will be the moderator here and after this discussion Dr. Mied will summarize the whole session, not only this session but the whole meeting and have some concluding remarks as well as the action items from this -- outcome of this meeting.

So with that I think what we -- I guess, I just want to first put a broad picture here and then open for
the discussion here. So what we -- the goal of this workshop really was to, as I said in the very beginning, that we had always asked this question when an emerging infection comes to the forefront and is a threat to the blood or tissue safety how do we prioritize and how -- what are the roles and responsibilities of the public health agencies as well as the stakeholders.

So with -- so the question here is the process of how we prioritize these things, how we react to that, and what we need to do that and what kind of information we need to gain -- get that. And so I think the challenge as we heard before us is the prioritization is not an easy task because, you know, as Dr. Epstein mentioned that when there are several things going on in the same time how do we prioritize. And there was a very good discussion by both Roger and Sue about how difficult it is to prioritize.

And then we heard very important, you know, this teeter-tottering between the scientific and epidemiological evidences versus the public perception and how do we respond to that. And so do we -- so that we are then transparent in our actions to be showing the
preparedness in that.

And so I think we also -- then comes the question of yes, we identify by -- we heard by horizon scanning maybe, we can be always looking at it, and the websites or the information published unpublished and then what is important, and what is not important we can figure it out, and then basically do the risk assessment and risk -- then obviously the risk management. Then we also heard that it's not just us in this country, it also the emerging infectious diseases are not -- don't have borders and barriers and it's a global phenomena. So we need to be very cognizant of how do we engage the global community and then, I guess, then what -- once we recognize those things what are the measures we can take to prevent that happening that these emerging infectious agents threatening the blood safety or tissue safety.

I think with that opening remarks, I think, we'll open for the discussion and I think we have maybe, Matt, you want to add something to that.

MR. KUEHNERT: I think you said it pretty well. I think that the process is the key and also, I think, some themes that I'd like to hear opinions about is how to
achieve both transparency and accountability so that the process is standardized and whether whatever pathogen we're talking about or biologic and that there is transparency throughout the process to everyone but also that there is accountability that we actually reach each stage of the process. Often times, you know, there is a committee recommendation of some sort and it sort of disappears until it appears back in the media and then it's dragged back out. So I think that's something that is important to me to see in any discussion.

MR. NAKHASI: All right, so I think with, I guess, we will, you know, I have put some standard questions here but I don't think we need to follow those exactly in those word-by-word but I think what we need to -- that's the overarching theme of what -- how do we prioritize, what's the role of public health agency and stakeholders to develop a threat -- response to threat for EIDs, what type of lessons we learned in the past experiences, and then what measures we should be taking. I think with that I will open it for panel discussion and then participation from the audience as well.

Roger?
MR. DODD: Well, if I get the first word in I can leave everything to everybody else and just relax but it occurs to me that prioritization in and of itself isn't necessarily all that helpful and we need a framework within which to prioritize. We need to know what we are trying to achieve and this is an area where we really don't have any guidance. We've accepted somewhere between strict application of the precautionary principle and as low as can reasonably be anticipated or achieved. And these are both very difficult environments in which to work.

And I suspect that some of us of my vintage remember what we thought was going to be a really wonderful meeting of the Institute of Medicine which was basically posed the question what do we do about infectious disease testing for blood and where do we stop and so on. And I think that what we were looking for was some sort of statement of what is acceptable risk. And I think that it was a wonderful meeting but at the end the Institute of Medicine in all its grandeur and glory looked out and said to us the blood bankers "Well, you're smart people, I'm sure you'll figure it out." And of course, we
never did and here we are again asking essentially the same question.

But I think unless we have a framework in which to put it we're going to continue to be floundering and it almost seems to me that there are two things that are missing and we should think about structuring one is that we're going to take a lot of the things that we heard about and perhaps develop almost some sort of scoring system. How many -- I mean, just to be perfectly blunt about it how many cases of transfusion-transmitted vCJD can society accept and is that going to be, and I suspect it would be, many fewer than how many cases of, for example, Babesia because we've talked about both of those. But we don't have the framework.

And the other thing that came up and occurred to me during the meeting and I thought was a very important comment was communication because I think that at least some of the issues we're trying to deal with are issues of interface between us the professionals, the blood bankers and you, the regulators, and the public. And it almost seems to me that we need a trusted and non involved communication mechanism. I don't know how we do that. Is

But how do we get, once we've got the structure, how do we get a message across that this is everything that can be done. This is what cannot be done and this is where we're trying to go. So far we sort of floundered around saying we're doing a process. And even we don't know what the outcome of the process is going to be. So that's more than enough.

DR. ALTER: I was so concerned (inaudible) that -- two things I'd say is one that once one can develop a multi pathogen chip where you can put 30 or more agents that you might be concerned about and do it on the same amount of blood at the same time then the question of prioritization becomes moot and the same thing would be true for pathogen reduction that this is only an issue before either of those things happen.

The second point is I would think that one could develop some sort of formula for priority which would be the prevalence of the agent times its transmissibility times the seriousness of the resulting infection. And I don't know what numbers those would be or what terms you
would use but it's got to be in that sphere. We're going to worry more about something that causes really bad disease. We're going to be worried about something that's very clearly transmissible. We're going to worry about something that is in a sufficient number of donors to make it a problem. And if you go back to HIV you could say well, what would have made us put HIV on the top of the list. Well, disease outcome would be number one priority. And the rest -- so that has to have a multiplier too, an additional factor.

MR. DODD: I think what you're suggesting Harvey, there is an example that in terms of devise development as part of design control process. We call it a "failure modes effects analysis" and you assess the very aspect of the things that you were describing. What is the frequency of an occurrence, what is the severity of the outcome? And then you develop mitigations to address that based upon the score. There are scores that are assigned to those and then you develop mitigating steps either through process improvements or through instructions for use clarifications that allow you to intervene and reduce the risk if it's above a certain
level or accept the risk that's there relative to the overall score, the OCD as it's sometimes called.

So I think there is a way to perhaps utilize that kind of an approach which does have a regulatory framework I believe associated with it in this kind of a setting as well.

DR. ALTER: You know that's exactly what I'm saying. Do you have a job for me in the industry?

MR. DODD: I just wanted to add that there are other acronyms that are available for that sort of analysis as well. One would be multi criteria decision analysis which would involve all the steps that you are talking about including the waiting step where we can, you know, express our values with respect to some adverse outcomes or positive benefits compared to others, so all these methodologies exist.

I think the question is getting -- there're two problems. One of them is getting consensus on our values and the second is dealing with the fact that we have incomplete information and can we deal with the fact that we could be wrong.

SPEAKER: I would just remind of how serious the
disease is as a criterion has a couple of components to that. One may be the catastrophic pathology itself in those individuals who succumb but it also can be, for example, like polio virus where a very small fraction of infected and exposed individuals will actually succumb to the overt and what's recognized as catastrophic pathology. And that could be a mitigating factor in terms of deciding the priority for very small fraction of individuals who are actually going to develop full blown Aids after an HIV infection. We have a different perspective on that as a risk. Unfortunately the situation has turned around.

There are remarkably few individuals who have favorable receptor genetics to provide a barrier to full blown disease. The second criterion that kept coming up as I listened to the other speakers was making this connection between the archived repositories of donor samples and recipient samples and what data there might be with those precious few pairs of samples, and trying to establish the transfusion transmissibility of the agent. And with the conventional diagnostics that are thrown at detecting and identifying agents there's virtually no way to differentiate a particular positive sample from any
other particular positive sample, whereas with a sequencing based approach, regardless of whether it's the platform I talked about or any other sequencing platform, when you have two or three genes or whole genomes of a pathogen from one sample and another you can forensically and epidemiologically track and establish with a much smaller number of samples the linkage that would establish transmissibility.

MS. STRAMER: Perhaps not as sophisticated as what Harvey alluded to in a quantitative model and that Ray elaborated on that can be used or is available through industry. I mean just going back to the AABB approach we could try to do although perhaps in precise and perhaps our assumptions weren't perfect. We tried to do prioritization in a quantitative way and although variables, science and epidemiology, although that one is probably the most solid of the two variables public versus science. We gave some kind of quantitative measure and initially when we did that we tried to give each, you know, severe, moderate, not severe, theoretical. We tried to give them quantitative measures. And my idea was to try to put them into an equation to come up with an
automated ranking so that we -- it would appear to be less subjective. But with the public perception it was a little bit more difficult. So we tried a rudimentary way to do that.

So I do believe when push comes to shove we did -- we're able to prioritize agents and I think anyone in this room probably would have selected the same agents as being the most significant or the most severe. I think the exercise is not so much prioritization but the question is when do we act. When do we need to implement an intervention for any agent whether it's prioritized or not, and then what type of intervention is introduced, and if the intervention is introduced does it have a reversible decision. So once it's introduced can we remove the intervention if we find that it's no longer needed so --

SPEAKER: Just on the area of prioritization there are at least -- I think there are two templates out there. One, if I remember correctly, is -- there's a textbook that came out a couple of years ago out of the U.K. Transfusion Microbiology that Roger knows. I think you wrote the preface for it but in the first chapter
there -- it's either the first chapter or near the beginning, they go through what they do in the U.K. And then have a huge checklist for each -- for agents and that they rate agents. I'm not sure if it's a numerical rating scale but it's a list of formal questions that they ask of each agent. And I don't know what they ultimately do with this but we could look to other -- we could look at that or what other jurisdictions have done.

And then secondly there is -- Simone Glynn has talked in some of her talks about this kind of prioritization agent being done for community-acquired infections and there is at least was an effort -- there's a paper, I don't remember the reference now that -- where they tried to do this. They took 10 or 20 experts in Germany or in Europe and tried to evaluate a set of communicable agents to see which ones they should be prioritizing. But lo and behold, not every expert saw it the same way. So people had the same data and yet they didn't necessarily interpret the data the same way similar to what Mark was saying because there are a lot of unknowns.

I mean, if we could quantify everything we could
come up with a formula but, in fact, we can't quantify everything. And so I don't know. I agree with Sue, I'm not sure that that's the main function. I think you get a sense for most agents whether they are important or not important. And I think we subjectively do that. We look at the epidemic potential. We kind of model in our own minds the worst case and we look at the public perception. I agree with Sue though that the -- once we do that then we get really hung up on the next stage and that is when do we assess that this is a significant enough risk to take an action. And I think maybe, we should be thinking about that more than prioritizing. And I'll let somebody else give the answer to that question because it's a hard one.

MR. NAKHASI: I think I guess that is the question. I think we heard this morning and you know we know that we can prioritize, because the transfusion manuscript and others and literature, and we heard the horizon scanning. But the question is here, I think, a big picture question is how do we get that thing? How do we get our arms around that process, that is, what should we be doing continuously to look at that events that when
that trigger is needed. Should we be looking together as the public health agencies, the stakeholders that's the blood establishment and the manufacturers, the public that when some kind of a system there which we'll be looking every periodically what's the status. And therefore we should not be digging well, you know, when the house is on kind of a fire here.

And so is there a process or is there a idea around the table and the public that how we could achieve that. And I would like to challenge Peter on that, how do they do, you know, like you in Canada or other places I know the situations are different, the laws are different, that things are different but at least if we have some idea of what triggers you to do those things, you know, maybe, there is some lessons learned.

DR. GANZ: Thanks, Hira.

Yeah, I think those are all important questions and I guess this is a good segue from what Roger commented on which his exasperation and surprise when IOM didn't sort of help with regard to providing a solution. I think we would have had a similar situation in Canada because I think the issue really is very complex and not as how do
we -- what is the form to engage the broader public and stakeholders in improving public health. And I'm not sure there's a single answer there.

I think there is -- because there is political dimensions to that as well and I don't know about the U.S. but in Canada our politicians play a very conservative game usually and are charged with some fairly heavy responsibilities as we are in the transfusion and transplant areas. And I think that they rely on us as experts to address those issues. Having said that I think we need to look at how we do -- looking at the past to learn from it and certainly I think a priority for Health Canada and or in terms of prioritizing EID issues, I think, we have sort of proceeded although we have -- don't have a formal recipe. I think Harvey's comment of bit of a shopping list for things in terms of is the infectious agent -- does it cause significant mortality and looking at the epidemiology of the agent and so on.

I think we take all of those into account in making those -- in making decisions about whether to act or not. And I think we do the same thing U.S. does. First of all, once the issue is identified I mean, you
know, you're having a blood products advisory committee on XMRV coming up in July. It was raised here and it's in the open public forum. So I think taking the issue to the stakeholders is key.

I think the only sensitivity I would have is, you know, is the timing for all of -- to do all of these things takes time, energy, and effort. And sometimes one has to risk prioritizing and say is the energy better spent in actually addressing the problem rather than trying to be all inclusive with regard to engagement. Recognizing that the public does have and the workshops we had West Nile virus there were two. We had one on Chagas testing and Chagas disease as well.

I think the feedback there has been they have been very happy with how we've approached the issues of EIDs and transfusion. And they, I think, there's more of a feedback in Canada for us doing things quickly. And certainly Sue's point is well taken in the sense that if we have an intervention how can we get -- can we -- is there an exit strategy for it.

And often I think that's where the regulator -- I think we need to do a little bit more work in developing
exit strategies for regulatory interventions. I don't think we've done a really good job with that. And even if we thought about it we haven't done that good a job in communicating it. So I think that's an area we need to do some work. So I'm reasonably comfortable with the process as we've defined it, the transfusion article I think has done the job of prioritizing it. I just think if we have our collective minds together I think we need to think more about how we in our respective countries can engage broader public health issues and engage the public in those.

We do have some funding from our Canadian Institutes for Health Research to look at public's views on new technology such as pathogen reduction technologies to see whether or not, you know, a patient's going to be given a choice. This is pathogen reduced and there may be some untoward consequences down the future or here's one that's gone through the standard testing as best we can but you take a risk with this. And we want to engage the public in understanding because I think there is an issue with introduction of new technologies and the public says well, I'm getting a unit of blood that's been pathogen
treated. I didn't have any say in that. Is there another option? So I think these are difficult issues because eventually we're going to have to bring them forward to the public.

And one final word really is relates to Roger's comment as well is what is risk tolerance? And a good example I can give is that annually we lose about a 1,000 Canadians every year to annual flu, okay. And these are healthy people unlike blood where you're giving product to people who need it because they have a particular underlying clinical issue. In vaccines, you're looking at normal individuals who are being immunized and the risk tolerance with a 1,000 deaths a year is such that there's not a lot of public outcry although there's a general problem with vaccines that lobby groups that think vaccination is not a good thing.

So in that situation is there -- if we try and look at that through the lens of blood transfusion and transplantation is that an acceptable level of risk to see thousands of people die every year. So we're managing issues down to one or two people being a problem and yet the public tolerance on the one side for another class of
biologics is much greater. So maybe we need to again readjust our communication strategies to say look, you know, blood is not zero risk and anybody who gets blood components are going to have to accept the fact it's not zero risk. And you know I think it's been driven to a large extent by attention to tainted blood. And we're still living in the legacy of that and perhaps it's time to move forward with different kinds of messaging.

SPEAKER: I just wanted to comment on that briefly. I think one could imagine a framework where you have a threshold for even consideration because that is going to take resources. So you know something like you think it's a one-in-a-million risk at that point you start a process. The other -- the elephant in the room that I don't think has been addressed is cost. Clearly that is a big inhibitor for a lot of discussions about test development, about implantation, about a lot of the issues. And I think that needs to be entered in the equation whether we're talking about an intervention or whether we're talking about the outcome.

So you know the cost of intervention, and also the cost of transmitting an infection, and the cost of
cure for that individual and the public perception of that may be very different. But because when you get a bacterial infection from a platelet transfusion and you die 2 days after I mean that actually can be much more devastating than an HIV infection that can be treated. So but that's something that can be put into a model with stark numbers and sort of take the subjective feelings out of it.

The other issue which I think really does change in terms of biologics is the safety versus availability issue. You know when there's a false positive on an organ donor screen the working assumption is that you have an organ that is wasted and a resulting death in someone who is on the wait list. And one can think that for blood if you have enough deferred donors that something like that is going to be in place. So I think that that also has to be put into the equation.

SPEAKER: Matt, I just wanted to expand a --
SPEAKER: There are two -- so two comments here, Jerry.

MR. NAKHASI: Harvey and then --
SPEAKER: Jerry has been waiting and I want to
say something.

MR. NAKHASI: Oh, Jerry, okay.

MR. HOLMBERG: Yeah, I just want to, first of all, say that I think that what we're missing here is that the -- and I think that Matt mentioned this to start with and that is I think the process is very important. What triggers the prioritization or the strategies for elimination are something else that has to be worked through but the process is very fundamental.

The other thing is that I appreciate what Sue did with the prioritization by not only putting the science in there but the societal. And I think that we don't pay enough attention to the societal. You know in the societal we have to be looking at the ethical implication of it. We have to look at the outcry. We have to look at how much risk does the community really -- is the community really willing to take. For instance, you know, there are acceptable limits for parts per million for different agents out there that we breathe or drink everyday. But yet for blood we've never taken it to that level of having like an EPA for blood, okay.

So I think that we have to go back constantly to
the societal aspects of things to make sure that not only do we have -- it goes back also to what Ray was saying with the teeter-totter, you know, you have the scientific on one side and you have the societal issues on the other side. And you can have a very squeaky wheel that really tries to alter the teeter-totter but the problem is do you have enough science or others to level the playing field.

MR. NAKHASI: Harvey.

DR. ALTER: Yeah. I was never good on a teeter-totter. I have a little bit different perspective for which I'm going to be beaten down. But I think we're putting a little bit too much emphasis on public perception. I think if you have an agent that you know causes bad disease and is easily transmitted then public perception shouldn't get into the equation or not very much. I think that's a scientific blood banking type decision. So at the end, when you have a ruling you might fly it in front of the public to see what the response would be but the basic decision is a scientific one.

It's when the data are marginal that the public perception may get engaged because if you have something that you know is transmitted but doesn't do much but the
public really wants it maybe, you'll make a different
decision or vice-versa. So I -- but I think it's a level
down for public perception but I don't face the public lot
so maybe that's --

SPEAKER: It seems to me that we actually have
two levels of decision making at least in the U.S. and
Hira, you kind of alluded to it. One is what does the
regulatory agency say that the community needs to do or
must do in terms of an intervention. So you know an FDA
guidance or licensure of a test and requiring blood
centers to use it. Once -- so when does the evidence rise
up to the level where FDA takes action. That's one
question. It's easier in a way because if FDA takes
action no matter what people think whether they agree or
disagree everybody does the same thing. But most of the
blood safety decisions that have been made in the U.S. in
the last 10 or 15 years have come outside of FDA
regulation. I mean even Chagas disease testing is
optional. Some centers do it and some don't.

So then you get into the blood banking community
making decisions and licensed blood establishments making
decisions that are not necessarily the same across the
board. And then the concept of cost really comes into the issue because basically hospitals don't want to pay anymore for blood. Hospitals have competing priorities on how to spend their money. Blood centers compete with one another to sell their blood to hospitals. We have plenty of blood right now. So competition is happening again. So I think you know there are issues -- so I think -- and there are a lot of voluntary initiatives that have been taken with safety in mind by at least part of the community. And you can argue whether they are necessary or not universal leukoreduction is one. Some centers have done it and others have not. Chagas disease is another, bacterial testing is another although it's a little bit more uniform now.

And I think -- so I think -- TRALI reduction by primarily male plasma, yeah. So I think the question is when -- so there are some actions taken but those actions involve a lot of other considerations. But when does FDA enforce an action? I think that -- when does a public health sector say, you know, there's enough decision making to regulate. So I do think we have two thresholds and we should put that on the table.
SPEAKER: I -- Sue, I think you made an excellent point. The fact that there is so much disagreement, there are so many unknowns, the fact that there is a list that prioritization has been done with those agents I think is a remarkable accomplishment. We can debate where things may go but clearly it's laid out. I guess the question would be and we're talking about process so XMRV comes along. What do you see as being the process to put that on the chart in its appropriate location? How would you proceed from this point forward?

MS. STRAMER: Well, our approach for XMRV was first to create a fact sheet. We didn't necessarily prioritize because I don't think we have enough critical mass yet or enough has changed to really look at all of the agents again and reprioritize. We did put public perception and scientific epidemiologic criteria within the fact sheet. And from looking at the definition to clearly fit into the yellow category. But we haven't thrown all the agents again into the mix and said, you know, here we are, we're going to start again, which do we still conclude.

Are the agents that have the highest scientific
and epidemiological threshold to act or those coupled with that have a high perception need to act? So I don't know, you know, and at what point the subgroup who works on that we make a group decision when it's time to reprioritize, when it's time to issue a new supplement. Probably it won't be this year. I mean, judging at how much, you know, work went into the original one we'll continue to update fact sheets, we'll continue to create new fact sheets as they come up. But anyway and I have another comment to make, the one related to what Ray just asked.

If we look back at the lessons, if we will, from the past 10 years or so or 20 years and say, you know, what have we done? The reason we have acted with the exception of vCJD and malaria which are questions that are mandated for us to ask donors. Most of the decisions we made or the actions we've taken have been due to the availability of a test. So you know part of why I see us sitting here now is the paradigm has changed for the test kit manufacturers. We don't have Babesia tests. We don't have dengue tests. I mean there probably will never be a test for variant CJD, thankfully.

But you know, if we had some of these tests
available today like we implemented T. cruzi testing, we did it as a voluntary initiative. But I think, you know, with the absence of tests or the absence of the commitment of vendors to step forward we really have to look at doing things differently. So I think now it is different than it was in the '80s, '90s or 10 years ago. So you know perhaps there are two manufacturers who are trying to get pathogen reduction technologies in the United States but outside of that I don't see any of our test kit manufacturers clamoring forward to bring us new tests. So what we have is what we have. And even if there is deficiencies in those tests I don't think it's going to be that easy for companies to say yes, I want to spend a couple of million dollars to fix my test. So I really do think we're at a really a breakpoint now where we have to look at things differently.

SPEAKER: Excuse me, if -- oh, go ahead.

MR. DODD: Thanks. I think one thing that struck me although Susan woke me up short with her comment in a sense it's been that at least in U.S. pretty much everything that we have done so far has been in the face of a disease and I was going to say always a disease that
has actually been transmitted by transfusion. And Susan reminded me of vCJD which arguably was such a horrible disease and was so clearly actually transmitted by some infectious process.

And I think it's very important to remember this as we talk about barriers and two agents that trouble me a little bit or a lot, forgive me Peter, are SFV, simian foamy virus and XMRV because we're really talking about taking action in an environment where we really don't have a disease that's clearly transfusion transmissible. We have a suspicion that these agents could be transfusion transmissible. We don't even have that confirmed. In fact, there's been a definitive look back on a donor who did have SFV infection, didn't transmit it. So I think we need to put this in context.

Now it becomes very difficult to do this when we have this apparently rather high public pressure to take action. But that's taking action based on somebody else's hypothesis. And it troubles me and many times I've run across people who talk about things like virus chips and they say wouldn't it be just be wonderful we can test every donor for everything under the sun. And I was
always brought up short by people who said well, but wait first, don't you need a disease?

And I think we need to make sure that we're chasing the disease, not looking at the agent and forcing it to be a disease agent. So this is a sort of barrier that we really hadn't discussed but I'm concerned about the direction.

SPEAKER: Harvey.

DR. ALTER: Yeah, well, I was going to say something very similar to Roger. I think this theoretical formula that I would have -- you can do the same by logic and eyeball (phonetic). But if you had a formula and you took XMRV we know a rough donor prevalence that we'd be okay there but we haven't yet proven it's blood transmissible. That information should probably be coming out soon. But we don't have a disease. So I think -- so that would turn your formula right now to zero but -- so that puts it into a very low priority based on science. That's where maybe perception would come in and then the perception would say well, maybe we should do something but something mild. You know, maybe ask a question or give more information to the donors. Those are mild
interventions which are commensurate with the risk. If it turns out that it really causes chronic fatigue syndrome that it moves up the ladder on your priority list.

MR. HOLMBERG: You know as I follow it that Harvey, I mean we do have a plan with XMRV now and that is to try to fill in some of the missing pieces, right. So at some point your intervention is to make that agent a research priority which I think was done very early on by HHS and you know we even came up with some money to fund some studies which unfortunately have been slow to get underway but at least recognize that this agent because of public concern and because of scientific reports was deserve -- at least made the radar screen to be deserving a further work. So I mean is that an intervention? I guess intervention is a wrong word because we haven't mitigated risk yet but we've put it on a priority list to take some actions that we wouldn't have taken otherwise so I agree with that.

SPEAKER: With a multiplex testing technology that's readily adaptable one of the least intrusive interventions you could take like for XMRV would be to put it on the screening list and start collecting data
ensuring that with the public side advocacy groups get a really strong handle on prevalence among donors, track recipients when problems arise and the data is there if and when a case comes up that it's been transmitted at zero extra cost. It's a piggy back just like a biothreat agent test on the backbone of dozens of others that are of higher priorities for which actions have already been identified by policy.

I also want to throw some fuzz into, for example, Susan's prioritization of pathogens with respect to their emerging infectious disease risk. I heard earlier in this discussion the word community strains of some pathogen or other and immediately made the pairwise connection to nosocomial strains. And there are people out there who have developed assays that purportedly distinguish nosocomial and community strains of staph or strep or any number of agents. But they almost always ignore the fact that the distinction is local.

There's nothing biological that distinguishes a nosocomial strain from a community strain other than the venue in which it currently is replicating and characterized. And then lastly, earlier in the talks
today there was talk about the milieu of antibiotic resistance genes as a potential emerging threat.

And one of the things we've learned from trying to address that with the highly multiplexed arrays and sequencing. We have a program with the University of California San Francisco looking at antibiotic resistance. We've picked up out of the GenBank at least 1,600, maybe 2,000 very, very distinct clades of different antibiotic resistance gene sequences.

And what's interesting about them is most of them are freely mobile from one host to another. So if you address these as emerging infectious disease related threats and try to screen for them and you have a focus on the particular pathogen genosome species or the particular virus type and subtype or serotype you may miss out on the fact that these things are freely mobile in between and you may not even be testing for the host of the particular resistance gene that still represents a threat to a recipient of that. But if subject for some bug you haven't tested for but is likely to be resistant to a palette of plasmid or transposon-borne resistance genes.

And so I think you need to be careful in this
realm of prioritizing EID threats not to limit yourselves to conventional Microbiology 101 definitions of pathogens. They don't hold up any longer. It's a much more complicated gene pool that needs to be resolved.

SPEAKER: I was just going to follow up on that that I mean I think from a scientific perspective it would be a great opportunity to look at a donor, screen them, they pass all the routine required screening tests but then do this sort of array analysis; find that there are 30 potential pathogens. The blood gets transfused because it passed all the tests. And then follow the recipient.

But I could imagine from a regulatory perspective the answer would be well, wait a second it's got these 30 things. There's no way that we're going to let that go through. And thus you're stuck. So somehow we have to get out of this frame of mind. I remember the quote from Dr. Busch (phonetic) that you know we have a viral flora in the blood just as we have bacterial flora in the gut. And I think if the public were able to learn that and accept it then I think we'd be in a different paradigm.

SPEAKER: I think that's absolutely true and one
of the things that can come from longitudinal testing with the kind of multiplex technology is a better appreciation for the individual personalized infectious disease picture that each of us brings to the table. I've had several respiratory infections over the last four or five years and yet my commensal flora H. flu, Neisseria meningitides nonA-nonB strep have been constant for 2-1/2 years in relative loads and in genotypes. But I've had metapneumovirus, rhinovirus and now most recently para-flu. That's what putting this testing into --

(Laughter)

SPEAKER: That's what putting this kind of testing into place can offer but at the same time, that's right that unless the regulatory policies that are in place based on what we have known to date evolve with what the facts of molecular life are teaching us with new technologies then we are going to be stuck. We are either -- you can do that but you can't tell anybody or you can't do that because nobody wants to know or you can only tell one thing at a time even though there may be 30 others. You know it's the mentality if you don't test for it, it clearly isn't there.
MS. STRAMER: (Off mike) -- I don't think anyone would argue if we could have high throughput or cost conversion of all of our screening platforms on to a chip, add any new pathogen that comes along, put one drop of blood on the chip and 10 minutes later we get the test result that interfaces with our quarantine processes to label blood. You know I don't think you'd have any argument from anyone there.

You know but then on the other hand, you've got to look at what point in time do we have too much information. You know we -- I mentioned 4,000 proviruses integrated in our own genome. So you know at what point do we say this is something that we should be screening for and this is -- whether it's marked viral flora or just avirulent organisms. Anyway so I --

MR. DODD: I was just thinking of a new pickup line, what's your flora?

(Laughter)

DR. EPSTEIN: Jay Epstein, FDA. I think we need to caution against setting up FDA as you know the obstacle to progress. I think FDA is a final pathway toward a mandatory requirement which essentially establishes
standards. And I take the point that was raised earlier, I guess, by Steve Kleinman that there really are two tiers you know there's a voluntary action and then there is regulatory requirements and that's true. And we are struggling with what's the threshold for a mandate.

But you know the FDA is capable of doing what's rational. It's just that we have an ultimate mission to make determinations of the -- where does the balance lie of risks and benefits. And sometimes that requires evolving new paradigms of scientific thinking and that's okay. But you can't expect it to be instantaneous because you know you have many standards that are already enshrined in, you know, statute and regulation and you can't just override the whole issue of how do you then integrate societal factors, for example, all of the standards that have evolved around research, you know, testing the donor for things you don't tell the donor you're going to test for.

You know there's a lot of experience with the ethical consideration down that pathway and it leads to the question of what is research versus what is standard practice. So I think all these issues can be tackled and
that we shouldn't think that just because the paradigm may
be new that therefore regulators are the barrier.
Regulators just have to develop another paradigm or they
are capable of doing so if it's in the public health
interest. I mean the reality in government is that it's
actually quite flexible. It's just that it's a
deliberative process and therefore it always seems slow in
the heat of the moment.

MR. NAKHASI: Mike Strong.

MR. STRONG: Just a follow up on that. We've
spent a lot of time here talking about responses but you
haven't really tackled the questions three and four up
there which Susan started on by saying what have we done
in the past and identifying these emerging agents the
responses have been quite different. The identification
of the problem has been quite different in concert with
this meeting since we're going to be talking about organs
and tissues tomorrow, remember that West Nile really was
first identified in an organ recipient through a organ
donation through a blood transfusion. So we are all
related in some aspects.

But I'm wondering about how do you see the
surveillance system working? Is it adequate? Is there more that we could be doing because you can't have a response until you identify the risk?

MR. NAKHASI: I think that's a very important point. I think that we need to focus back again whether we react or proactively are, you know, at the heat of the moment are we are we -- preparedness. And I think that's where the whole process is to -- because how do we -- I want to go back to the same question which I started with. What process can we keep in place besides, you know, with no prioritization and all those things. What are the things like horizon scanning, surveillance epidemiology, risk evaluation. You know we have to do it continuously these things so that then when the threshold reaches then we could react to that. Otherwise what happens is, you know, either we succumb to public perception or when there is a -- it's a no-brainer when there is a scientific -- there is a lot of evidence and scientific evidence of epidemiological evidence vis-a-vis with the disease or with the transmission. Then we can quickly react to that and the regulatory bodies will say okay, we would like to have a test.
But it's that gray zone when we do not know what the risk is, for example, we are struggling with this XMRVs issue now and I think that's where we need to have some kind of a process where we could continuously -- today it's XMRV, tomorrow maybe Q fever. I don't know what is going to be down the lane. So I think we need to have as a collectively whether it's the stakeholders, whether public health agencies to have a constant dialogue and which we are having through the AABB taskforces and other things that and BPAC presentations and other things that we got to have that constant evaluation of those agents so that when a threshold is reached then we react otherwise it becomes a chaotic process. At least it looks like outside people to them, it looks a chaotic process.

SPEAKER: Here if I can just use an example I think that you know the XMRV is an excellent model. And I think that what we've done so far with XMRV has been very deliberate. You know the literature came out a couple of years ago with XMRV and in prostrate cancer. And then most recently in October of last year it was the XMRV and relationship with individuals with chronic fatigue syndrome. So what we've done right now is very deliberate
process of trying to standardize the procedures along the way. We've identified that there are things that we have to tweak such as sample preparation, the time for preparation.

And so now I think that what we've laid out even this morning was the idea that there are repositories, okay. So we don't know whether it causes disease in man. We do know about the trigger that really got us thinking was that it has the potential of being transmitted in the blood. It is associated with white cells. There are certain amount of the viruses in the plasma. So because it has the potential for being transfused -- transmitted then that really got us going. That was one of the triggers.

Now the deliberate process that we have is that we have to be able identify it in a standardized way and then also to see does it cause disease. Now as Harvey mentioned because it's unclear there's no clear-cut scientific then the societal issues are weighing in and the pressure is then what are you doing about this. And how much risk would the society be willing to take. So I think that maybe, we have an opportune time here to take
XMRV as the model process and really work our way through on how do we handle these for the future.

MR. NAKHASI: Have that luxury to do that because, you know, the thing is yes, we are doing it and there are processes but at the same time if their public perceptions getting stronger and stronger what do we do in that. So that's the discussion we're having that we are having a deliberate process. We are doing systematic way and then at the same time, you know, we have a public perception and public pressure from certain affinity groups as was pointed out how do we react to that. I think that's the key.

SPEAKER: Well, I'm not sure, Jerry because I don't really know if we know enough about XMRV to declare it to be the model and you know we may find ourselves in the same position as we were with swine flu so many years ago not this one. We may find ourselves in a very different position. I think the one model that was very interesting since Mike brought it up was West Nile virus. In actual fact it wasn't a huge surprise to us to find transfusion transmission and I don't think although it might have been recognized through the transplant
mechanism.

You'll remember that Lyle Peterson and Brad Biggerstaff somewhat had tweaking had already taken the effort to develop a model that said that there was a certain likelihood of transfusion transmission and that paper came out about two months before reports on transfusion transmission. So we were actually prepared and we had been through a process, we'd been through a process where we'd identified a rapidly spreading pathogen. We had considered in general that it didn't fit out at that time pattern for a transfusion transmitted agent.

But we nudged somebody into thinking a little bit harder to calculate, if you like, whether it was going to be and it was there in nine months of that event we had a test in place. And arguably it's been a very successful program. It's much easier to look at the models in retrospect than in prospect but a lot of the stages that we've talked about were actually there. We had a disease. We had an infection. We had an accurate picture of the epidemiology of this thing. We knew it was expanding and going to cause a problem.
We asked a question should we really think about it as transfusion transmitted. And when we found it was we were ready to act pretty quickly. Maybe that isn't enough for today's days -- today's time but I think the right aspects of the model are there.

SPEAKER: Roger?

MR. DODD: Yeah. I agree it's a very good model but the -- but, in fact, instead of going into the 2000s we were with West -- here we are now with XMRV is where we were in 1999 when West Nile virus first hit New York. And I think that's where we have to go back to and it was five years before the test was in place. So once we had the proof it moved very fast. But from the first recognition of the virus as -- and looking at that epidemic that suggests that it might be transfusion transmitted. So in one respect we did great but the other respect we were late. And maybe if we had a more active model about that time we would have done better.

SPEAKER: Well, I want to go back to when West Nile virus was in West Nile Valley because I think that's the horizon scanning issue that I really am concerned about because when you think about XMRV we started to
really give it attention when the science article came out about the association with chronic fatigue not when it was associated with prostrate cancer. And the Q fever example, you know, when we were asked to do a risk assessment for European CDC then it got on our radar screen but not really before that.

So my view on horizon scanning is it really doesn't matter what your regulatory structure is in your country or how your government is structured. It's just the collection of data and we can all do that together globally. There's really no excuse not to do that. I mean, we can use, you know, Google Translate and the language barrier is not an issue either.

We should all be able to have the same methodology and yet we don't. We rely on, you know, phone calls from colleagues or e-mails or publications which is way too late to take action. So I would just urge all of us to try to figure out, you know, it's not what everyone in the room is expert in bioinformatics but it's something that I think we need to take a close look at just as we're looking at other things that we're more comfortable with concerning repositories and epidemiology.
MS. STRAMER: At the same time if we do that clearly at that point in time if we're looking at Uganda and -- or the West Nile Valley in 1937 there will have to be a way to prioritize because there are hundreds and thousands of viral or bacterial or protozoan agents, you know, for which we do nothing. I mean, I do think we need to take a step back and say we have done a reasonably good job. You know, I don't think there have been a lot of transfusion related deaths due to infectious diseases but we aren't aware about that we could have taken some kind of prevention for it but we didn't based on the fact that they may have been a lower priority agent.

I just wanted to go back to something Harvey said earlier about taking action when the science is there and science being the main driver versus public perception being less of a driver. So we go back to Roger's topic XMRV versus Babesia. We have an agent that has very high scientific reason to act and we're not. We spend most of the time on this panel talking about XMRV. And whether you say 0 to 4 percent is prevalent in our donor population it's probably transfusion transmitted. It is retrovirus. We still have no intervention for Babesia and
it doesn't matter what we say up here.

The test kit manufacturers aren't interested in making a test. So we can say we need to do a, b, and c but the only tools we have are donor question or some kind of health deferral. And a donor question is not a simple thing to do, I mean, it has to be developed, procedures have to be written, training has to occur, we've got to make sure we're doing it effectively. We have to determine what needs to be asked.

I mean is it a medically diagnosed case of XMRV? If we say that then we're missing 85 -- I mean of CFS. If we're doing that then we're missing 85 percent of undiagnosed CFS cases. If 4 percent of the donor population carries XMRV and doesn't have CFS even if we put a CFS question in, I mean, what benefit will it have? Anyway, so I'm just venting.

(Laughter)

MR. NAKHASI: I think -- but I think that's an important point here, Sue. I think we -- what we are missing is the other stakeholders which is the -- our manufacturers of these test kits that we need to have somehow convey that message that, you know, when we are
prioritizing an agent which you just said Babesia where we know that it's a definite disease associated in transmission and whereas the, you know, XMRV may be so-called at this point hypothetical and -- but then we need to have that group also engaged and are there ways to engage that group to you know -- of course, I hear, you know, bottom line is money and as many times Jay would -- suggest, Dr. Epstein would suggest that, you know, we need to have a some bigger picture here from the, you know, in other -- as other countries have that national testing laboratories and things like that where they could do those things.

And therefore, you know, if the company is not interested in developing a test for a small market what would it take to do that. And so I think that's another, you know, sort of equation we need to put this in this perspective.

SPEAKER: A new paradigm would be if FDA punishes companies who make bad tests FDA should punish companies who don't develop tests that we need. I had it.

MS. GALEL: I'm Susan Galel from Stanford University. Just I want to make one comment about this
issue of test implementation, test development which brings us to question three, what lessons have learned from previous experience. And I just wanted to point out that although the 1980s included a lot of bad experiences in transfusion medicine there were also a lot of, I think, good experiences that we can and should learn from.

One is CMV seminal studies and CMV transmission were developed using studies using tests that were diagnostic tests. And in fact, I believe, CMV tests are still not licensed as a donor screening and yet I don't think there's any question that we've improved safety for recipients using tests that did not go through the licensure process. Similarly the implementation at my facility of T-cell subset testing and core antibody testing and other facilities, I believe, was scientifically based -- was based on science available at the time and in retrospect did reduce transmission of HIV and also nonA-nonB hepatitis in the case of core antibody and the core antibody test results are not FDA licensed at that time.

So I think that it is worthwhile considering other models that we've used in the past and in the case
of Babesia I think it's a reasonable model to consider to use either a diagnostic test or ASR test that might have — might be scientifically based and yet not perfect from the perspective of a potentially licensable test.

SPEAKER: I had a question. I wanted to follow up actually on something that Dr. Ganz mentioned in his presentation. He talked about ways that we might be able to facilitate the introduction of new interventions. And perhaps that goes to number three and number four and one of those was for example, indemnification. You mentioned that and I was wondering if you would elaborate on that. And then another question I had is that in considering the implementation of interventions do factors such as at-risk populations, groups that might be at greater risk, let's say, from using Babesia as an example from receiving a transfusion that's tainted versus someone who is immunocompetent and may not have the same reaction.

Is there a role or a way that you could consider the implementation on a more limited basis of interventions that with at-risk populations where you would have criteria to determine if they fit or they didn't fit and is that a way to limit therefore the spread or the
exposure perhaps from the risk of the intervention if there should be downsides.

And I'd be interested in just hearing what the panel had to think about that but in the indemnification Dr. Ganz, if you could --?

DR. GANZ: I guess, I did raise it as a question and I guess the only real world experience is in the, again in the vaccines area and for example, you know, for our H1N1 response it, you know, our role in the federal government was to provide leadership in protecting the public from H1N1 and the pandemic and we did fund a manufacturer to develop the vaccine for us.

And so there was an arrangement with costing which is really the other end of the discussion we had in terms of, you know, how important cost is in funding. So I guess really in terms of rounding up the discussion and to tie-in to blood would also be whether or not what should the role of various governments be in providing incentives to industry, you know, from the point of view of public health, the public health agenda, and maybe that's an area as well that can -- needs some further thinking and discussion in terms of how do we -- you know,
if the barrier is well, you know, if Babesia is important and it's prioritized and we feel that there is a public health value added to implementing that test, you know, what incentives can be offered forward to industry to develop tests.

And then I guess as well is what the other part of equation isn't just industry it's the operators in blood centers, you know in terms of implementing the test and purchasing the tests. So it isn't just the costs of the tests, taking it through licensing and so on. It's also the issue of within the blood center budgets, will they pick up and do the testing for that. So that's another part as well that fits in.

Again, in terms of the broader question that Dr. Goodrich brought up is really one of accepting risk and if there is a risk to new technology what responsibilities should government have in accepting some of that risk in the interests of seeing that the intervention that is proposed might have public health value and then maybe a downside as well. So that's really, you know, it's sort of like moving a mountain a little bit to get the governments to understand. But I see it as being in the
government realm.

MR. NAKHASI: I guess if anyone has a burning comment --

SPEAKER: Well, I just wanted to say I think what is holding up a lot of progress in things is a lack of confidence in knowing about outcomes in transfusion recipients. I think if we had robust hemovigilance systems in the United States and throughout the world we'd have a lot more ability to be able to look at the impact of pathogens. You mentioned West Nile virus, we're talking about dengue. I mean what are the actually the outcomes of transfusion transmitted infections in recipients. For Babesia actually we have a pretty good idea and it's not a good outcome. So there I think there's an argument to really make an intervention if we were able to compare, you know, apples to apples in -- with a robust hemovigilance system I think we'd be able to make clear decisions.

MR. NAKHASI: All right, I think with that I think I would like to thank all the panelists -- no, no, no you're not going anywhere because --

(Laughter)
MR. NAKHASI: Paul is still going to summarize for us the last -- you know the concluding remarks and from after that we'll adjourn.

I think this is a very important thing to listen to him and -- because these are the action items which we'll be following.

CONCLUDING REMARKS

MR. MIED: All right, thank you.

Well, we started out this morning with the goal of exploring strategies for EIA threat detection, intervention, and the prioritization effort. We wanted to describe how we characterize and should characterize the risk from emerging infectious diseases that are relevant to blood safety and how we prioritize and should prioritize our response to those EIDs. We acknowledge that this has always been a complicated process.

When it comes to preparedness given multiple EID agents that threaten blood safety it can be a challenge to prioritize our efforts to address the risk and we acknowledge that there is no single approach or formula
that guarantees an ideal prioritization process. And I think this panel discussion brought out that point very well.

When we speak of emerging infectious diseases we're referring to new reemerging or drug resistant infections whose incidents in humans has increased within the past two decades or whose incidents threatens to increase in the near future. We've heard outstanding talks today from expert speakers. And I can only attempt to hit some of the highlights for you or at least some of the major points that I've heard. And I apologize to our speakers if there are any major points that I missed.

But we heard this morning about the many diverse factors that contribute to the emergence and spread of infectious diseases such as physical environmental factors, genetic and biological factors, ecological factors, and social, political, and economic factors. Among these are human demographics, behavior, and sanitation.

Closer human contact with wildlife and its habitat, failure of control measures, international travel and commerce which results in population movements and
transport of agents, reservoirs, and vectors, microbial adaptation and change, human susceptibility to infection, climate and weather, and even lack of political will and complacency.

We emphasize the importance of public health surveillance in being prepared. Now surveillance is the ongoing systemic collection, analysis, and interpretation of outcome specific data which needs to be closely integrated with a timely dissemination of those data to those people who are responsible for taking public health action. About 70 percent of our 68 or so EIDs have been zoonotic, that is, able to transmit from animals to humans with wildlife being an increasingly important source as reservoirs for vectors for disease, and new threats will emerge many of which will be zoonotic.

The key will be to unite human and veterinary medicine, to anticipate potential threats to blood safety and to be vigilant with early detection, improving our predictive capability, and improving coordination and communication. We have learned from recent outbreaks that for this we need strong national and international partnerships including multidisciplinary and
transdisciplinary collaborations that include the human and animal public health sectors.

We looked at various current effective methods of horizon scanning, that is, the systematic examination of potential threats, opportunities, and likely developments and the ability to detect novel and unexpected issues, persistent problems or trends.

Horizon scanning complements evidence synthesis and we looked at various examples for EIDs. We learned about the characteristics of the current repositories of specimens that have been established through the years and the specific purpose for which each one was established, especially the large scale TTVS, radar, and trips linked donor-recipient repositories. We heard about the contributions of each repository and being so valuable in allowing for the evaluation of transfusion transmission of known agents and that may be very useful for that purpose for new and future EID agents.

We were told how these repositories are maintained and given useful information regarding how and when to access these and what criteria need to be fulfilled to access these linked donor-recipient
repositories for future studies of transfusion transmission of EIDs such as potentially for XMRV studies.

The critical information about a particular EID comes from answering such questions as is the agent blood borne? Is there an asymptomatic blood borne phase? Have transfusion transmissions been observed? Does the agent survive component manufacturing and storage? Does the agent cause disease? And what is the disease attack rate? What is the severity, mortality, and treatability of the disease? What is the donor prevalence and incidence? And is it significant? Is there a professional regulatory and public concern? Are interventions available? What would be the impact of those interventions on resources?

To explore these questions further we looked at two case studies for Babesia and XMRV, two agents that are at different stages of the decision process. We know that Babesia is an emerging transfusion transmitted infection that is expanding geographically and regional testing is conceivable. For XMRV on the other hand, no transfusion transmission has been observed. There is no known causative relationship to disease and the donor prevalence is unknown. The literature is controversial. With
inconsistent findings for viral markers and test methods have not been standardized.

However, Canada, Australia, and New Zealand have donor deferral in place for a donor who volunteers to have a history of diagnosis of chronic fatigue syndrome. It was mentioned that the precautionary principle is one tool that has been used in making decisions. The current perception of the precautionary principle was stated as action should be taken even if its value cannot be proven, that is, even if there is only a theoretical risk of harm. If risk is possible then we must err on the side of caution, but as was pointed out that that action must not be disproportionate. The question to focus on is how to prioritize? And we've asked this question of our panel this afternoon.

An EID agent priority matrix which showed public or regulatory concern on the Y axis versus scientific evidence of blood safety risk on the X axis led to the suggestion that dengue virus, Babesia, and vCJD should be the EID agents that we should prioritize for intervention. These prioritized red agents have in common that they are known to be transfusion transmitted, they are increasing
in worldwide frequency, they cause disease in recipients, and there are no specific interventions for them. In the end the question is what's the appropriate action now?

Implementing blood donor testing for Babesia is an option that could be considered but for XMRV we could continue research and perhaps consider implementing an interim blood safety intervention until the main questions about XMRV as an EID that could threaten blood safety are answered.

We heard a description of the AABB, TTD, EID four-year project with the goal of doing three things, first to describe known and potential EID agents for which transfusion transmission is documented or its potential exists and no effective intervention exists; two, to create fact sheets for these agents and three, to prioritize agents as to their blood safety threat. We were left with challenges to consider. Several profound questions such as should the target be zero risk or evidence based? What to do about lack of interest in participation from the manufacturers due to the small market and margins? And where will the funding come from as threats emerge or current technology becomes
We learned about risk assessment that it has components such as hazard identification which is easy for some EIDs but not for others, a dose response assessment for the infectious agent, an exposure assessment in which parameters are represented as distributions and not as point estimates, and risk characterization. We were told that risk characterization is a synthesis of all that information that estimates the health effect of exposure with uncertainties in a form that risk managers and stakeholders can understand and use.

Risk management considers risks and benefits and compares potential mitigation what-ifs such as how does the risk change by testing all donors or some donors or by changing the questionnaire, et cetera. And the number of cases prevented for each mitigation for the emerging blood borne threat.

We learned about the existing decision making framework that Health Canada has for managing risks such as EIDs. Six interrelated steps that may be grouped into three phases, first of all, issue identification, identify a possible risk to blood safety; secondly, risk assessment
such as donor risk of exposure by surveillance and
hemovigilance and benefit assessment and three, risk
management in which options such as testing are identified
and analyzed, a strategy is selected and implemented and
then the results are monitored and evaluated.
Implementing surveillance measures to assess residual
risks to the system.

Two key questions were raised question number
one, should there be greater international collaboration
in managing EID risks? That's the second time we heard
that today. Risk management is multifaceted and a global
enterprise and as the way forward we need global partners
in managing strategies to address EIDs. We need stronger
links with other governments and regulatory authorities
and public health to manage EID risks. We need increased
networking of researchers to form better linkages with
governments and global coordination of responses to EIDs
in the area of blood safety. We need collaboration and
communication with our domestic and international
stakeholders to prepare for new EIDs and new technologies
to combat them. And we need a forum to describe how the
decisions that were made were made.
But question number two was asked what is the appropriate vehicle or process to put this into action? The tests array high multiplicity, resequencing pathogen microarrays were described as cutting edge technology that would enable high sensitivity multiplex detection and specific identification of dozens of the highest blood product and tissue safety priority level pathogens as a single test of a single specimen with same day results.

We learned about measures that have been taken to reduce the risk of transmitting spongiform encephalopathies such as sporadic and variant CJD by human blood and blood products. Measures for managing the risks of contamination in medical products and the current FDA approach for viral clearance validation studies of human plasma derived products that serve as precedent for TSEs. We also learned about the latest technologies for prion protein assays and blood filters that are under development.

And we heard about the contrast between expectations and realities for pathogen reduction technology and for diagnostic tests. The realities include, for example, that development costs for new
diagnostic tests can average $30 million per test. And for pathogen reduction technology methods can average $500 million per method. The three principles protecting from transmission of pathogens, donor exclusion, testing, and pathogen inactivation and removal were examined for their advantages and limitations. The perceived costs for implementing pathogen reduction technology have until now been countered with the potential benefits of lower infection rates and eliminating some current tests.

This approach was questioned. It was suggested that combining methods may offer advantages (inaudible) process approach involving two independent methods was presented that combined NAT and pathogen reduction technology to cover the window period.

Could testing plus inactivation or removal equal reduce costly deferrals? The suggestion was made to consider where and when it makes sense to apply pathogen reduction in combination with or in lieu of testing or deferrals. The point was made that no decision can ever be without risk. One method can't be perfect or solve all of the problems nor does it need to be.

Those are the major points I heard from the
presentations today. I can hit some of the major points that the panel just raised because in our roundtable discussion this afternoon we attempted to chart a path forward. Where do we go from here?

We really wanted to draft recommendations and an action plan but in trying to get these answers to these questions that we have here I heard even more questions asked.

(Laughter)

MR. MIED: I guess that's the nature of this business. Some of the comments we heard were that prioritization in itself is not all that helpful. What we really need is a statement about what is acceptable risk. We need a framework. Two things are missing we need to develop a scoring system, for example, how many cases can society accept? Secondly, communication between industry, regulators, and public, we keep hearing that over and over today. We need some mechanism for communicating what can be done and what can't be done. Can we develop a formula for prioritizing, for example, prevalence times transmissibility times severity of the resulting infection and develop mitigations based on the score? The AABB
approach which they tried to prioritize quantitatively severe, moderate, et cetera and they tried to put them into an equation but more difficult to factor in was public perception and societal concerns.

The exercise is not necessarily prioritization but when do we act with an intervention. And when it's introduced can it be removed if it's no longer needed. The question is how do we know when a trigger for action is reached. Also what is the forum to engage stakeholders in public health? But it was pointed out that that takes time away from addressing the problem. This process is important but what triggers a prioritization?

Go back to that same question. It was pointed that we have two levels of decision making. What do the regulators say must or should be done and also most blood safety decisions come outside of FDA regs or recommendations. These are voluntary initiatives by blood establishments. If we look back to lessons from the last 20 years we actually have acted because of the availability of a test. The paradigm has changed for the test manufacturers. If we had tests available we wouldn't have to do things so differently as we're trying to do
them today.

It was pointed out that everything we've done has been in the face of a disease. For SFV and XMRV we don't have a transfusion transmitted disease that we can identify. We need to be sure we're chasing a disease. For XMRV we don't have that. If it causes chronic fatigue syndrome then it moves up the ladder. So that has been made a research priority, XMRV. So really it's on the priority list for action already.

If the public could learn that we have a viral flora in the blood just as we have a bacterial flora in the gut we'd be in a totally different paradigm. The question was asked at what point in time do we have too much information, for example, about our viral flora that was detected. It was suggested that XMRV is an excellent model. What we have done with it so far has been very deliberate in trying to standardize the procedures, sample preparation, et cetera. We're asking does it cause disease? Is it transfusion transmitted? But because the science is not clear then the societal issues weigh in. It was suggested that XMRV is a good model for the future.

The counterargument was made that we may not
know enough about XMRV to declare it to be the model. We have a model, West Nile virus. Peterson and Biggerstaff developed a model saying it's likely to be transfusion transmitted and nine months later we had a test in place. So the stages were there. Disease identification, infection the picture of epidemiology was there so that was a very good model, West Nile virus.

It was stated that XMRV is where West Nile virus was in 1999 and we were a little bit late. If we had an accurate model we would have done better. We can all collect data globally and have the same horizon scanning methodology, but we don't. We need to look at bioinformatics closely. Also we've talked about taking action when the science is there but we still have no intervention for Babesia.

The test manufacturers are just not making the tests. When we are prioritizing an agent how do we engage the test manufacturers? What would it take to develop a test for a small market? And lastly, the question was asked can the government provide incentives to industry to develop tests and for the blood centers to implement those tests?
Dr. Nakhisi, I think I'll stop there and turn it back to you.

(Applause)

ADJOURNMENT

MR. NAKHASI: Thank you, Dr. Mied. I think you did an excellent summary about the whole -- workshop, and I want to thank you on behalf of everybody. I think it's time to adjourn this meeting and thank you everybody for their input. Thank you.

(Whereupon, the PROCEEDINGS, were adjourned.)

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