DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

74th MEETING

Thursday, September 12, 2002

8:00 a.m.

Hilton Silver Spring Hotel
8727 Colesville Road
Silver Spring, Maryland

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Temporary Voting Member

Liana Harvath, Ph.D.

C O N T E N T S

C O N T E N T S (CONTINUED)

P R O C E E D I N G S

Welcome, Statement of Conflict of Interest

DR. SMALLWOOD: Good morning. Welcome to the 74th meeting of the Blood Products Advisory Committee.

I am Linda Smallwood, the Executive Secretary of the committee. At this time, I will read the Conflict of Interest Statement that applies to this meeting.

The following announcement is made part of the public record to preclude the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the Committee Charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed Dr. Liana Harvath as a temporary voting member.

Based on the agenda, it has been determined that there are no products being approved at this meeting. The committee participants have been screened for their financial interests. To determine if any conflicts of interest existed, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has

prepared general matters waivers for the special government employees participating in this meeting who require a waiver under Title 18, United States Code 208.

Because general topics impact on so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Toby Simon is participating in this meeting as an Industry Representative acting on behalf of regulated industry.

With regard to FDA's invited guests, the agency has determined that the services of these guests are essential. There are interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants.

For the discussions on the Window Period HIV Cases and Current Estimates of Residual Risk, Dr. Michael Busch is the Scientific Director, Blood Centers of the Pacific. He has grants, receives

speaker fees and is an advisor for firms that would be affected by the discussion.

Dr. German Leparc is employed as the Chief Medical Officer for Florida Blood Services. In addition, listed on the agenda are speakers making industry presentations. These speakers are employed by industry and thus have interest in their employer and other regulated firms.

FDA participants are aware of the need to exclude themselves from the discussions involving specific products or firms for which they have not been screened for conflict of interest. Their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask, in the interest of fairness, that you state your name, affiliation, and address any current or previous financial involvement with any firm whose products you wish to comment upon.

Waivers are available by written request under the Freedom of Information Act.

At this time, I would ask if there any additional declarations to be made from any meeting participants.

Hearing none, I would like at this time to introduce to you the members of the Blood Products

Advisory Committee.

Members, when I call your name, if you would please raise your hand.

Dr. Kenrad Nelson, Chairman. Dr. Stuver. Dr. Allen. Dr. Harvath. Dr. Lew. Dr. Doppelt. Dr. Klein. Dr. Fitzpatrick. Dr. Fallat. Dr. Simon. Mr. Rice. Dr. Laal. Dr. McGee. Dr. Koff. Dr. Schmidt.

Announcements

DR. SMALLWOOD: Before we proceed with the formal meeting, we have two retiring members leaving the committee at this time, and I would like to ask Dr. Jay Epstein, the Director of the Office of Blood Research Review, to come forward and to make the presentations to Mr. Terry Rice and Dr. Toby Simon. If you would come forward, please.

DR. EPSTEIN: It is my sad pleasure and privilege to be awarding plaques in recognition of the years of good service that have been given to us both by Mr. Rice and Dr. Simon as members of the Blood Products Advisory Committee.

We know that it takes substantial effort on the part of the members to read the voluminous packets that we send you on very short notice and to deliberate long and hard on the many difficult

questions that we bring before the committee.

I just want to express the thanks of the Food and Drug Administration to each of you for the work that you have done these last couple of years, and we do hope that you will agree to say on as special government employees, so that we can also tap your expertise ad hoc from time to time.

Thank you very much.

[Applause.]

DR. EPSTEIN: These are also letters of appreciation.

DR. SMALLWOOD: I would just like to remind everyone that this is a one-day meeting of the Blood Products Advisory Committee. We have a very full agenda today and we will try to adhere to our time range as best as we can. We would ask that when it is time for your presentation to be made, that you be prepared, and if you have a presentation for which you will need assistance with our audio-visual group, would you please let them know.

At this time, I would like to turn over the proceedings of the meeting to the Chairman, Dr. Kenrad Nelson.

DR. NELSON: Thank you, Dr. Smallwood.

The first part of the agenda is a series of summaries of workshops and of other evolving issues. First, on the agenda, is Virginia Wanamaker summarizing the Advisory Committee on Blood Safety and Availability meeting that was held about a week ago.

Summary of PHS Advisory Committee on Blood Safety and Availability Meeting, 9-5-02

Virginia Wanamaker

MS. WANAMAKER: Good morning. I am pleased to be here this morning to tell you a little bit about the Advisory Committee on Blood Safety and Availability that met last Thursday, September 5th, and the topic of our meeting was how can government and industry work together to assure the availability of blood and blood products.

There were actually two issues at the meeting, the first being the CMS proposed rule on new payments for outpatient services, and the other was the blood supply.

So, right away, fairly shortly after the meeting started early in the morning, the committee proceeded with two recommendations. One of the recommendations was for HHS to direct CMS to establish 2003 Medicare hospital outpatient

prospective payment system payment rates for blood and blood components, transfusion services, and the transfusion laboratory procedures based on the current year acquisition and actual total cost rather than hospital outpatient claims from previous years.

Then, there was another recommendation relatively similar, but this one addressed payment for plasma-derived therapies and their recombinant analogs and that they be based on current year acquisition and total actual cost of providing such products and services both within hospitals and non-patient settings to include physicians' offices to assure patient access to care.

From that, we moved on to looking at the blood supply. There were actually two components of this. One was monitoring of the blood supply, and the other was to look at the question how much is enough. We also, at the end of the day, had a brief updating on the West Nile virus, but I believe that is on your program and I will just merely mention that and move on.

In the Monitoring Section, we heard from about five monitoring systems that are currently in process.

The first was the Department of Health and Human Services monitoring system, which is a sentinel site blood monitoring project. This project has 26 hospitals and 3 community sites. It collects quantitative data.

From this project report, it appears that the overall supply, especially from these sentinel sites, is adequate, however, there are a few of these sentinel sites that have chronic issues or chronic shortage problems.

The next was FDA's TransNet. It is not yet fully functional, but it is a web-based plan with daily entry. It has various markers of shortage. There will be a daily--once the web site is up--there will be a daily map displaying areas, and it will highlight the areas with shortages. This is a qualitative system with no quantitative data.

Next, we heard from ABC, America's Blood Centers. My understanding of their system is that it is a two-phase system. The first phase monitors the day's supply. The second phase will show members areas of access, however, to date, they have mostly had shortage issues, and that is mostly what they are displaying.

Then, we had a presentation from the National Blood Data Resource Center. There were about four points from their presentation, that total collections information 2001 were over 50 million units; more surgeries were affected by shortages in 2001 than in 1999.

The collections and inventory total so far this year are unchanged in comparison with last year prior to September 11. By the year 2020, there will be 12 million people added to the age group that are at risk for transfusion. NBDRC believes that long-term quantitative monitoring is an essential part of the blood monitoring system.

We also heard from the American Red Cross. They manage inventory across 36 regions. They consider a two-day supply to be critical inventory, and they did fall to this level at the end of last month. They do consider a seven-day supply to be optimal.

We had a small session on forecasting, which actually was an overview of the monitoring programs. The speaker or the presenter favored quantitative programs or the need for quantitative programs. He actually liked the sentinel site, and he did state that a shotgun effect, if you have a

lot of different monitoring systems, and they approach monitoring in various ways, that they give you a comparable end result, then, they are doing a good job.

We also heard from the Department of Defense on strategic reserves, that there are problems with frozen reserves, and a liquid reserve on a national basis would be advantageous to all.

There was a suggestion that there would be four to six sites throughout the U.S. located near large international airports or large military bases.

Then, we moved to session of how much is enough. We heard from Puget Sound Blood Center, which says that about two-thirds of the blood they collect is used in the Seattle metropolitan region, the other one-third goes to surrounding counties, and they can export small amounts.

We heard from Georgetown University Hospital on the hospital perspective. The point here was stressed that appropriate usage is a very important issue, and that their oversight is driven by educational programs and that blood utilization reviews play into this. The speaker did point out that platelets can sometimes be an issue.

Then, we heard from the New York Blood Center, who says they continue to struggle with the aftermath of 9/11. They have lost some of their blood drives due to loss of offices or companies that participated in these blood drives. They continue to struggle with the CJD deferral, the summer slump, and self-deferral of some donors.

We heard from the Oklahoma Blood Center, which said that really blood serves two purposes. One of the purposes that we don't really speak to are addressed quite often, but is very significant and very important, is the availability of the blood.

Even though blood is not used, it is still an insurance policy that allows for a procedure to occur. Quite often a unit of blood may never be used, but it may have been cross-matched three or four times, so it has indeed served a purpose because it was available for those medical procedures to go forward.

The presenter did tell us that their blood center supplies 89 hospitals with 11,000 units. They have in excess a 17-day supply with their liquid, and they are moving to having a frozen supply that will allow them to have a 23-day

supply.

We heard from the Mississippi Valley Regional Blood Center, which says they are able to supply their hospitals with a 5-day supply, keep a 10- to 12-day supply in their center, and export up to 50 percent of the red blood cells they produce.

After that, we move to Recommendations. These, of course, are paraphrased. One of the recommendations was that the Department should support initiatives to improve management of blood inventories--I am sorry, I skipped the first one--that DHS should promote increased public awareness of the ongoing need for routine blood donations by healthy persons, and this could be done through periodic public service announcements, visible blood donations by top officials, and paid advertising campaigns, also by funding of demonstration projects, supporting specific initiatives to encourage routine donations by young persons and minorities, and play a leading role in increasing participation of federal employees in donating blood.

Another recommendation was that DHS should maintain and/or increase funded support for blood supply monitoring. Some of the ways to do this

would be long-term trends in blood collection and use or some of things that should be done, should be addressed.

Data on daily national distributed blood inventories, indicators of blood shortages and excesses, predictive models to identify trigger points for coordinated national donation campaigns, and coordination of government and non-government initiatives.

There was another recommendation that has not yet been voted on, but I will go ahead and mention it to you, that DHS should support initiatives to improve management of blood inventories. This would include defining the roles of liquid into frozen reserves and by integration of supply forecasting into intervention strategies, and also strategies to facilitate movement of blood from areas of surplus to areas of shortage.

I failed to mention earlier, under the "how much is enough," that we also had a presentation from American Red Cross, and they did mention that they monitor some 36 sites and that on occasion, it has fallen to a two-day supply.

Actually, that is my presentation for today. I notice that many of the speakers are in

the audience, so I would like to take this opportunity to apologize if I misquoted or missed the point of your presentation, but I thank you very much for his opportunity, and I hope I did highlight the main points of the meeting.

DR. NELSON: Thank you.

Any question or comments? Toby.

DR. SIMON: When these discussions are held, for the most part people tend to forget that in the late 1980s, there was a program called the National Blood Resource Education Program that was funded by the National Heart, Lung, and Blood Institute. It was designed to use the same techniques that the institute had used for awareness on cholesterol and high blood pressure, for awareness on blood donation. They created a huge advertising campaign. There were ads in airport billboards, and other such things, and it was largely regarded as a failure.

So, I think if we are going to move forward or if there are recommendations to move forward, I would suggest that people look back at that program and try to diagnose the problems it had before investing in a similar program in the future.

DR. KLEIN: I just wanted to comment that there was one other presentation that you didn't review. After the major blood organizations reported surprising shortages, especially over the past two months and especially in terms of O-positive blood, and the New York Blood Center told us that they were transfusing increasing amounts of O-positive to O-negative patients because they didn't have sufficient supplies of O-negative blood.

The American Hospital Association gave us what I thought was a very startling page of data, which included the fact that of their 5,000 transfusing members, some 57 percent had delayed surgery during the past year because of unavailability of blood, and that in urban areas, 77 percent of their membership had delayed surgery because of lack of blood for transfusion. I found that startling.

DR. ALLEN: A question for any member of the blood banking community that might have an answer. My guess is that most people, when they donate, do so with a certain sense of civic responsibility and under the assumption that their blood probably is going to be used in the

geographic area. The Puget Sound Blood Center was mentioned, the majority is within the Seattle area of surrounding counties, and I suspect that that is what most donors would expect.

Is there a reaction on the part of donors if they understand, if they are in an area where there is excess red cells being collected, that it may be sent anywhere around the country? Does that tend to defer people from coming in to donate, and is that an issue that needs to be addressed as we look at the supply and distribution of blood?

DR. SIMON: The general rule over the years is if you educate donors about that, they are agreeable to having their blood used for anyone who is in need. So, as long as people have been educated appropriately, this does not seem to be a serious issue.

DR. FITZPATRICK: We heard an excellent report from Iowa at the meeting on a community blood center that produces an excess and exports, and the community is very supportive of that. I think there is proven community blood centers that are able to do that.

DR. EPSTEIN: I think that we have not really looked strategically at what I would call

large system issues, and I think one of the points that came across I mean clearly in a disaster, it is obvious that there is enough blood out there, in other words, there are enough qualified donors if you can bring them in.

It has been said by many people that the crux of the matter is investing in recruitment efforts, but then that has a collateral effect on raising the cost of blood, and then we have, on the other side, problems with reimbursing any additive costs of blood, and I think that we haven't really looked at the economic issues that affect the whole issue of trying to bring in donors and that it is sort of an unspoken part of the problem.

DR. NELSON: The cost of blood has really increased quite a bit recently. It was interesting that there was a mention of the reimbursement for that. I don't know if that is a continuing problem, but the cost has certainly increased, yes.

DR. SCHMIDT: One often forgotten point in relation to what Jim Allen and the other statement is that local blood centers are not really operated by their CEOs who see this big picture, and if they are operated by their boards of directors, who are local citizens who are charged with having enough

blood locally, but also cutting down the expenses or looking for other sources of income over expenses, and shipping blood out to a place like New York and supplying hospitals can bring income to those blood centers, so policies are made by those people and we generally just talk to the CEOs who, when they go home, they may hear a different story from their board of directors.

DR. FITZPATRICK: Just to follow up on Jay's comment, while we know that there are plenty of donors available and that we can collect the blood after a tragedy or a disaster, the key element is that we have to have it available, on the shelf, at the right place, at the right time to meet the needs of the disaster, and 24 to 48 to 72 hours later is not the solution to the problem. The solution is having it available at the time we need it.

DR. NELSON: The second item, if there are no more comments, is the summary of a workshop, an important workshop on pathogen inactivation. This was held in August at NIH.

Dr. Vostal.

DR. SMALLWOOD: While Dr. Vostal is coming, I would just like to apologize to the

speakers. We are having some obvious technical difficulties. I am told that this LCD is not accepting the signal from the laptop, so we are trying to secure another one, hopefully, very shortly.

Summary of Workshop on Pathogen Inactivation

August 7-8, 2002

Jaroslav Vostal, M.D., Ph.D.

DR. VOSTAL: Thank you. Thank you for this opportunity to share with you the summary of a workshop we had in August. The title of the workshop was Safety and Efficacy of Methods for Reducing Pathogens in Cellular Blood Products.

The objectives of the workshop were to review the different approaches to evaluating efficacy of pathogen reduction methods in cellular blood products, to establish the appropriate methodology for testing efficacy, to obtain consensus on what is the minimum level of efficacy required, to discuss appropriate evaluation of toxicity of the methods, and that is toxicity to the cellular product, as well as to toxicity to the recipient of the treated cellular products, and finally, to summarize the risks and benefits of using the pathogen-reduced cellular products in

clinical situations.

The outline of the workshop. The workshop was presented over two days. On the first day, we had an overview of the pathogens found in cellular transfusion products and the risk of transfusion-transmitted diseases from these pathogens and the ones we focused on were bacteria, viruses, and parasites.

We then had an overview of the molecular mechanisms of pathogen reduction systems. Then, we had a discussion on the evaluation of efficacy for the methods against each class of the pathogens, and this was followed by a panel discussion.

The first day ended with a presentation from the manufacturers, and they presented their own data on their individual systems.

On the second day, we focused on toxicity. We started off with evaluation of toxicity to the cellular products, and we focused on platelets and red cells, and each session was followed by a panel discussion.

We then moved on to an overview of toxicity and carcinogenicity evaluations for biologic products as is usually done by FDA, ad this was also followed by a panel discussion.

Then, we had two talks on risk-benefit analysis, and this was followed by a public comment period.

So, to get into the actual summary, for the transfusion-transmitted pathogens, it was pointed out that bacteria posed the highest risk, and the risk of a serious adverse reaction is probably somewhere between 1 per 10,000 to 1 per 100,000 platelet transfusions.

For viruses, the transfusion-transmitted risk is a lot lower. It ranges somewhere between 1 per 1 million transfusions to 1 per 5 million transfusions when these products are screened by NAT testing.

Of interest was that the window period viral load can be very high, up to 10^8, 10^{10}, and 10^{12} particles/ml for HAV and B19 viruses, and also interesting was that low levels of virus maybe at 10^2 genomes/ml can transmit disease.

For parasites, it was noted that these are emerging diseases that we should be concerned about. An example is Chagas disease, which there is 1 in 25,000 donor seropositive for Chagas disease, and 63 percent of these are parasitemic.

We then moved on to a discussion of the mechanisms or overview of the mechanisms of

pathogen reductions, and it was pointed out that all methods involve addition of a chemical to a cell product that interacts with nucleic acids to kill the pathogens. All are therefore potentially mutagenic and carcinogenic. They also bind proteins and lipids, which may lead to unexpected toxicity to the product itself or to the recipient of those products.

They do reduce the titer of extracellular or intracellular envelope viruses, however, their activity against non-envelope viruses is less defined. They can increase the titers of bacteria and parasites in blood, however, they are not effective against spores or endotoxin.

The next session was a presentation or several presentations followed by discussions on the efficacy against viral agents. It is difficult to capture the discussion in a summary like this, but I will just try to point out some of the statements that were made.

It was agreed that treatment will not eliminate current testing. The treatments may have potential to inactivate new and emerging pathogens not detected by testing, and they should have capability of 6 to 10 log reduction in the viral

load based on the window period loads.

Again, it was pointed out that low levels of viral load can transmit infectivity, therefore, it would be good that the methodology would have excess pathogen kill.

There was a discussion about a need for standard methodology for testing efficacy, for example, to define log reduction per ml of product, for the total bag of product.

Then, we moved on to a session with bacterial pathogens, and some of the points made in that discussion was that contaminants are most often skin organisms, but donors with occult bacteremia contribute significantly.

Both gram positive and gram negatives are associated with fatalities. Gram negatives produce endotoxin and do not require extended storage to reach toxic levels. Therefore, to eliminate these, the treatment needs to be pre-storage.

In terms of what bacteria should be used to establish efficacy, it was suggested that a limited list of bacteria is sufficient. The list should include the most commonly found organisms.

Finally, the clinical isolates of the bacteria should be used to model real life

conditions.

We then moved on to discussions of toxicity to the cellular product, and I am going to summarize the discussion that went on for both platelets and red cells.

This evaluation is usually done in three parts. The first phase is in vitro studies, and it was pointed out that in vitro studies have limited predictive value for in vivo performance, and they should serve as a screening method for identifying gross damage to different aspects of cellular function.

In Phase II, these are small clinical studies. These are usually done with radiolabeling and reinfusion of controlled and treated cells. Recovery and survival and circulation post-infusion are the readouts of these experiments.

There was a discussion on the necessity for establishment of uniform control and for platelets, this was considered to be fresh platelets, and a discussion on the minimal acceptable values for recovery and survival of these products.

In Phase III clinical studies, these will be large clinical studies that look at the function

and some of the functional endpoints of these products should be bleeding for platelets and oxygen delivery for red cells.

These kind of studies should also follow kinetic endpoints, such as transfusion response and frequency of transfusions.

We then moved on to a discussion on evaluation of toxicity to the recipient of these products, and this was a presentation to demonstrate how FDA reviews toxicity in general and to get advice on whether this is appropriate for pathogen-reduced products.

So, we covered general toxicity studies for biologic products, and these are usual animal models in small clinical trials. We talked about genotoxicity studies, which are aimed at identifying gene mutations and chromosomal aberrations, and usually, this required two in vitro studies and one in vivo study.

Carcinogenicity studies usually require a long-term carcinogenicity study in rodents, usually up to two years. We are moving towards using transgenic animals, which shorten that period down to six months. CDER guidances are available for design interpretation of these studies.

These products will likely be transfused to pregnant women, so reproductive toxicity is also an issue, and reproductive toxicity is studied in three phases. The initial phase evaluates toxicity to fertility, in general, reproductive performance.

This is followed by the second phase is a teratological study in rodents and non-rodents, and this will be followed by perinatal and postnatal toxicity in rodents, a unique toxicity that may be associated with these products with the generation of immunogenicity, so we had a presentation that dealt with how to evaluate this.

This is actually a difficult problem for not only these cells, but for other products. We found out that immunologic response to novel entity is not dose dependent and response could be to the original compound, metabolites, treated cells, or treated plasma proteins.

Animal models for immunogenicity may not be relevant to humans, and it was pointed out that this may be a low frequency event, it might not be detected in preclinical or clinical studies, and that postmarket surveillance would most likely be the way to attract these problems.

Another unique toxicity that may be

associated with these products is toxicity to the health care workers. These individuals will be handling high concentration of the chemical compounds and may be actually the highest risk population when these methods go into clinical use, and safeguards need to be in place for their protection.

So, then, we moved on to the final portion of the workshop, which was a risk-benefit analysis, and we had two talks. I think the main point was that the blood supply is very safe, as it is today, that bacterial contamination is the highest infectious risk, but there are other risks, such as medical errors, that are even 10- to 100-fold higher risk category.

The chemical treatment of blood decreases effectiveness of the transfused product and adds toxicity to the recipient that is not clearly defined. Pathogen reduction may be appropriate for certain patients, and the use pathogen-reduced products should be a medical decision, not a regulatory decision.

Finally, the cost of implementing universal pathogen reduction should be weighed against other approaches, such as bacterial

detection.

So, that concluded our workshop. I would be happy to answer any questions.

DR. NELSON: Questions? Toby.

DR. SIMON: This may be a question you can't answer, but can you give any further guidance timewise as to when we might expect to see such technologies be approved and come into use?

DR. VOSTAL: It is difficult to say because there are problems on the company side, as well as on the regulatory side, in terms of review, so I would say we are still maybe five years away from routine use.

DR. FITZPATRICK: Based on the meeting, do you see the need to revise or change any of the guidance documents that are currently used by industry to develop the path for submission of applications for these products?

DR. VOSTAL: I am sorry, I didn't catch the first part.

DR. FITZPATRICK: Based on the meeting, do you see the need for FDA to revise or put out different information regarding any guidance documents that industry uses to submit applications for approval of these products?

DR. VOSTAL: I think that is a good suggestion. We have certainly covered a lot of area in terms of how to evaluate platelets and red cells, so we have a platelet testing guidance we would like to update with that information. We would also like to put together a red cell guidance to have a similar type of thing.

Of course, we do not yet have a guidance for pathogen reduction, and that will be very helpful to have for other companies to follow, so based on what was presented at the workshop, we will try to put something like that together.

DR. NELSON: Thank you.

Next, our two speakers are going to review an emerging issue, mainly West Nile virus and blood safety.

First, is Dr. Marfin from the Division of Vector- Borne Infectious Diseases from CDC.

Dr. Marfin.

West Nile Virus and Blood Safety

Anthony Marfin, M.D.

DR. MARFIN: Good morning. I apologize to people. I see a lot of familiar faces. This is very similar to the talk that I gave last week, but I promise you there is going to be updates of

numbers, and I promise you that there is even some new maps in there.

[Slide.]

Here is the order of topics. I will just say a few things briefly about the virus. Then, I am going to talk about the viremia infection, the antibody response. I am an epidemiologist, so you know that I am going to talk about the epidemiology because that is what has really predominated our time in Fort Collins anyway.

With regards to the epidemiology, I am going to emphasize the geographic spread over the years since 1999 with special emphasis on the 2002 epidemic, which we are probably in about the middle of. Then, I am going to talk about a special case that we have been investigating with regards to confirmed West Nile virus infection that occurred in organ transplant recipients.

[Slide.]

West Nile virus is a flavivirus. Flavivirus is a big family, but there are only a few human pathogens. Most of the human pathogens are, in fact, arthropod-borne other than hepatitis C.

Specifically, with regard to West Nile

virus, it is related to yellow fever and dengue, and these are classic human pathogens. They can achieve high viremia and I should emphasize here that they have never been associated with a transfusion-related case of illness.

West Nile virus is only distantly related to hepatitis C. West Nile is part of the Japanese encephalitis serocomplex, and there has been a similar virus, an almost identical virus, that has been in the United States since 1933, when there was an outbreak of about 2,500 cases in St. Louis, St. Louis County, and the surrounding areas.

Almost all the members of this serocomplex, there is eight members in the serocomplex, and all of them are primarily bird viruses. They make birds sick, that is what they do. Human beings, horses, we are not an amplifying host that we know of. We have never served as a reservoir for any of these eight in the Japanese encephalitis serocomplex. We are merely incidental hosts.

Despite that, the West Nile virus since its introduction in 1999 into New York City has caused quite a stir, and I am going to show you why.

[Slide.]

Just a little about the infection. I want to emphasize this because this is the part that has somewhat been lost over the past few weeks, and that is, essentially all infections in the United States are due to mosquito bites.

Over the years, there have been infections that have occurred in the lab either due to percutaneous injury or inhalation, but I want to emphasize that when I get to the numbers, that almost all of those are due to mosquito bites.

With regards to the incubation, illness onset usually occurs about two to six days after infection. Again, these are measured in settings where the infections are due to mosquito bites. There may be some variation if we identify new modes of transmission.

The bite will occur. You get local viral replication. You get more replication in the regional lymph nodes, and this has been studied extensively in animal systems.

There is supposed to be a primary viremia in which the virus will spread from the regional lymph nodes to seed and replicate in the liver and spleen. This has not been demonstrated in humans,

it has been seen in animal systems.

Then, there is a secondary viremia that leads to invasion of the central nervous system, and it can result in febrile headache, which we call West Nile fever specifically. It can result in aseptic meningitis or it can result in encephalitis.

An important part when speaking last week and this week to people that are interested in transfusion is that the second viremia lasts five to six days, and this has been shown primarily in studies from the 1950s in Israel, as well as some experimental evidence from human beings also done in the fifties in cancer patients where the West Nile virus is being used as a therapeutic agent.

One of the problems when you look at these studies, especially the ones in Israel in the mid-fifties, are that this peak viremia occurs the day before illness onset, and that is not helpful to people who are wanting to have clues as to whether somebody is infected with West Nile virus.

[Slide.]

We have been involved in some recent West Nile fever studies in Louisiana this year, and we have screened approximately 250 people who

presented to a health care facility with headache, fever, and no other identifiable source of infection.

In those people, we have collected an initial serum sample, measured it for IgM to West Nile virus, but in addition, we have used NAT to see if there is any West Nile virus in there, and they are currently being set up for culture.

We have had the opportunity to identify three seroconverting people, people who had no evidence of West Nile virus infection on their initial testing, and then two weeks later, have IgM antibody to West Nile virus.

In fact, some of these people progressed to encephalitis, which is a relatively new finding. We have always assumed that people declared themselves. When you get infected and then you go on to illness, you are either in encephalitis, meningitis, or febrile headache.

In fact, we have measured people that go from the febrile headache to the encephalitis, but one of the things we haven't been able to do is we haven't been able to measure any viremia in these seroconverting people.

They initially present to us. There is no

IgM in their blood, and when we put them through our TaqMan testing, we are not able to demonstrate the presence of any sequence due to the West Nile virus.

In fact, isolating virus in the United States since 1999 has been very difficult. We only have one documented human isolate.

This was from a person who had very low levels of immunoglobulin and, in fact, NIH and the State of Maryland were able to make several isolates from this gentleman, and it is my understanding that he recently died despite treatment with intravenous immunoglobulin that was sent to the NIH center from Israel, and the Israeli population and immunoglobulins from Israel tend to have a higher concentration of antibody to West Nile virus.

So, I am going to come back to this last point, and that is, that in the fifties, when you go back and you look at these studies, especially the Israeli studies, that, in fact, humans develop a very low concentration of virus, about 10^3 or 10^4 virus per ml.

Our primary method of diagnosis for West Nile virus over the years--and it is kind of old

hat for a lot of people who want to use Taq polymerase--is serology.

When I came to the Division of Vector-Borne Infectious Diseases, we still had to learn about complement fixation and hemoagglutinin inhibition, and I am glad to say those are gone, but now we rely primarily on looking at viral-specific IgM and IgG, but I am just going to summarize it by saying that with regard to the flavivirus, this can be a problem.

Despite those problems, about 95 percent of people will develop West Nile virus IgM antibody by the eighth day of illness, and something that we have seen at least empirically, and we are going to have to look at it a little more closely, is that as the IgM titers go up, the viremia rapidly drops.

[Slide.]

I actually did this on the plane two days ago, so you will pardon those curves, but what we are able to see in the green line is that the viremia is peaking just before the illness onset. Illness onset is shown by that dotted white line.

By the first or second day of illness, that IgM is coming up rapidly. In fact, it is almost the rule given the sensitivity of our

serology testing now, that when people come in with illness, that we are already able to demonstrate that they have IgM to West Nile virus, so that goes up rapidly.

It peaks at about day 14 to day 21, and then it starts to decrease. What we have seen, at least in our New York City cohort, is that about two-thirds or three-fourths of those people are still going to have IgM antibody in their blood a year to two years later. That makes a little bit of a problem in terms of attributing last year's infection to this year's presentation of encephalitis.

Then, with regards to the IgG and neutralizing antibody, which is primarily IgG, this usually starts to rise about the fourth to sixth day, and then it peaks about day 21, and then it lasts for a lifetime, and is supposedly protective for the rest of their life.

[Slide.]

Here are many diagnostic methods. There has been much discussion that there are no rapid diagnostic tests for West Nile virus. In fact, there are rapid tests. The truth of the matter, though, is that they are not ready for the use in

large-volume industry, such as the transfusion industry.

We do have West Nile virus antigen detection. This is primarily used for insect pools, and we are now going to start using them in terms of testing animal tissues, and it is simply a dipstick, we also have an ELISA, and it detects about 10 plaque-forming units per 100 lambda.

We have amplification testing. We have both traditional RT-PCR and then we use TaqMan PCR, and for people that are not familiar with that real-time PCR, it involves the science of both Taq, as well as a probe that is chopped away, and then has a fluorescent signal when the components become liberated from that probe.

With TaqMan, we are able to identify virus if it is present in this concentration as low as a 10th of plaque-forming unit per 100 lambda, which is about equivalent to 50 copies per ml.

In addition, of course we still do virus isolation, which is not rapid, but for West Nile, it is rapid compared to some of the other ones that we have. The virus that we have in this country will come up positive in cell culture in about five to six days.

Most of the other flaviviruses with which we work are up to two weeks, and sometimes will not grow at all. They are very, very temperamental. This virus does not seem to be. We also have immunohistochemistry in which we use both polyclonal and monoclonal antibodies to demonstrate the present of antigen in affected issue, and then, of course, the serology.

Our classic serologies are IgM capture ELISA, IgG ELISA, and then the plaque reduction neutralization assay.

[Slide.]

With regard to the epidemiology, then, we know that the human infection rate correlates well with the mosquito infection rate in the Culex, BC's Culex, the urban Culex mosquito, the northern house mosquito, the southern house mosquito drives this epidemic. Although they are primarily bird vectors, they can develop such an infection rate that they can also bite horses, humans, and other mammals, and that is when we get into an epidemic situation as we have this year.

From studies especially in Bucharest, in 1996, we know that infection rates are roughly equal across age groups. We also know that because

of the work that we have done with regards to St. Louis encephalitis especially in Pine Bluff in 1991.

We know that illness, and this is meningoencephalitis, primarily affects people who are 65 years and older. We have looked at infection rates in this country. We have done four serosurveys, and these things are exhausting, so we try to stay away from them, but there was one done in the Hot Zone of Queens in 1991, and it was demonstrated that 2.6 percent of the population had evidence of recent West Nile virus infection.

I should point out that the survey area was extremely gerrymandered to look at the maximum seroprevalence rate that could be achieved. That is not a seroprevalence rate for the entire borough of Queens.

In 2000, we had serosurveys in Staten Island, Suffolk County, and in the southern part of--well, in Greenwich and Stamford townships. You can see that we had less than half a percent Staten Island, we had 0.1 percent in Suffolk County, which is on Long Island, and in Stamford, we were unable to demonstrate anyone that had a recent West Nile virus infection.

As I pointed out to the people last week, I was part of all three of these serosurveys. I literally walked the neighborhoods and birds are falling out of the trees. I mean there is an epizootic of undescribed proportion going on. There is crows that are dancing in the middle of the street everywhere.

These two were hot zones at least from an epizootic standpoint. In that year, though, there were only 10 human cases reported from Staten Island. There were no human illnesses reported in Suffolk County and then in Connecticut site.

[Slide.]

This is part of the problem when we talk about West Nile virus. Very few people--and that is the very top of this triangle--very few people develop what we call meningoencephalitis, and this has been show repeatedly. It has been shown in Bucharest in 1996. It was shown in Volvograd in 2000. We have shown it here in the United States since 1999. The Israelis have had a similar problem over the year since 1998, have also shown that only a few people that are infected develop illness.

In fact, what we find is that ratio is

about 1 to 150. For every 150 infections, you will get about one case of West Nile meningoencephalitis. For every 150 infections, you will get about 20 to 30 cases of what we call West Nile fever - fever, headache, myalgias, flulike symptoms. All the rest of the people are going to be asymptomatic.

They are going to have good antibody response. To the best of our knowledge, their viremia is the same as the top. In fact, the only difference is that you see that there are host factors that can account for this progression to West Nile meningoencephalitis. One of the ones that you will see discussed often is age.

So, when we are talking about the top of the triangle, we are talking about primarily older people. When we are talking about the bottom of the triangle, asymptomatic infections, these are primarily younger people.

[Slide.]

Let me talk a little bit about the epizootic.

[Slide.]

In 1999, infected birds were reported in 28 counties. This is when the virus is first

introduced into the country.

[Slide.]

In 2000, 136 counties reported infected birds. These are birds that people picked up and actually demonstrated the presence of virus.

[Slide.]

In 2001, there were 328 countries. You are seeing a theme here as it is moving centripetally.

[Slide.]

Let's talk about the components that led to this year.

[Slide.]

In 1999, human infections--this is meningoencephalitis--human illness, meningoencephalitis, was reported from six counties.

[Slide.]

In 2000, we now are talking about 10 counties, but it has really not moved out of the New York City metropolitan area.

[Slide.]

This is the growth year here. In fact, 39 counties reported human infections, but you can still see this primarily along the eastern

seaboard. It is maybe spreading a little to the west, down in the south.

You will see one county down in Louisiana, Jefferson County, in which there was one case reported, but as you will see in the later map, this was a harbinger of sorts.

[Slide.]

So, these are the human cases from 1999 through 2001. In 1999, despite intensive investigation, only 62 cases. In 2000, we are bringing on almost every state east of the Mississippi to find cases. Only 21 cases identified. Last year, there were 66 cases from 10 states in 39 counties.

I will take the opportunity now to show that, in fact, the illness onset date is very long for this disease or for this epidemic. The earliest onset in 2001 was the middle of July, but the latest was just before Christmas, and that is not unusual.

We have cases from Massachusetts in late November, so it is not just the addition of the southern states.

[Slide.]

Again, a summary of any activity in the

United States, and we will go right to 2001. Last year, there were 28 states or 358 counties in 28 states, and you can see that samples were collected from the beginning of April all the way until the day after Christmas.

[Slide.]

So, where are we now?

[Slide.]

This is as of yesterday, so this is the update from last week. There are now 42 states and the District of Columbia that report any West Nile virus activity in animals. There are now 30 states and the District that are reporting human West Nile virus illness. This is fever or meningoencephalitis. Now, we are up to 1,201 human illnesses that were reported. This includes 46 deaths. Approximately, 60 to 70 percent of that 1,200 are due to West Nile virus.

If you use that 150 to 1 multiplier, we are talking, in these 42 states and the District, we are talking about 100,000 to maybe 130,000 total infections. Those are not illnesses, those are infections. As I pointed out, about 80 percent of these infections are going to be completely asymptomatic.

So, in terms of illness, it is relatively rare. When you start doing the multiplication by 150, numbers add up, but when you put it over 42 states, it is still not all that frequent. We are not talking about influenza here.

[Slide.]

Here are the maps and here are the birds as of two days ago. You can see that the birds are predominantly being reported from the north central states. You can see several red areas especially up in Cook County there in Illinois, Harris County down in Texas, that is where Houston is, where they have hundreds of positive birds that they have been picking up.

[Slide.]

This is the map for horses, somewhat of a different area. Again, the red areas are the areas where the most horses have been reported, and you can see this is northern central, but a little further to the west. In fact, many of these counties don't have any positive birds at all, as you can see when you compare this to the map before.

The first illness is a horse. Now, why is this important? Mosquitoes that bite horses also

bite humans. They are mammalophilic as opposed to ornithophilic. People that live in these counties are at risk. There are not a lot of people that live in these counties, though, these are relatively low density except for my county right there in Colorado.

[Slide.]

These are the human cases. You can see that the human cases have spread way out of the New York City metropolitan area. In fact, when you look at the southeast, where in 2001, that is where a lot of our activity was, we have really shifted. We are now in the Mississippi River delta.

The hot areas right now are, in fact, Houston, Texas, New Orleans, Jackson, Mississippi, Memphis, St. Louis, Chicago, Detroit, and Cleveland, right up the Mississippi River Valley. In fact, that is roughly the way that they were reported to us, ascending northwards along the Mississippi River Valley.

By the way, this map here looks a whole lot like 1975, St. Louis encephalitis outbreak, and we are predicting that that is the kind of year that we are going to have this year.

[Slide.]

So, what are the problems? We have widespread and spreading activity. We have focal hot spots. It is not continuous. Again, this is not influenza. Activity can persist in a given area. Something I didn't mention earlier is that Suffolk County has had West Nile virus infections in humans reported four years in a row. That is something we haven't experienced a lot with St. Louis encephalitis for the most part. It is a relatively low human infection rate when you put that 100,000 over 41 states.

Other problems are the peak viremia occur prior to the illness, 80 percent of infected people are asymptomatic. Most of the symptomatic people are older and a lot of the are ill and not necessarily in your donor population.

The most important one, like almost all the other viruses in the JE complex, they cause unpredictable, sporadic, and epidemic infection patterns, so that is a real problem.

[Slide.]

Let me just say something about the West Nile virus infections in the organ transplant recipients, which has pulled my division into making presentations at meetings like this. We

don't do a lot of blood transmissible agent stuff.

[Slide.]

In late July of 2002, an eventual organ donor was in a motor vehicle crash. This person was a resident of the southeastern United States and from an area of moderate enzootic activity and low human activity.

During the first 24 hours, there were valiant attempts to save this person, and that was surgery and massive transfusions. The person then survived another 18 hours until they harvested her organs and during that 18 hours, they were preparing the person for organ donation.

There were five tissues that were collected. The two kidneys, the liver, and the heart did eventually go to four recipients. In late August, three of these four recipients had developed West Nile virus encephalitis. This is confirmed, there is no question that they developed infection, and one of those people died.

Just recently, the fourth recipient was confirmed to have West Nile virus fever, and that is recent confirmation, in fact, they all developed illness approximately the same time.

[Slide.]

Two of the four cases had outdoor exposure after transplant. They went home. They went home to areas where there were mosquitoes biting. They went home to areas where there was enzootic activity. They went home to places where there might have been a human case. So, they have some outdoor exposure.

They were residents of the southeast United States, but these two people did not receive any transfusions before their illness. The other two people had no outdoor exposure, they never went home after their transplant. They, too, were residents, so if they were to have received their infection at home, they would have had to have been done quite a bit before their hospitalization, but they are residents of enzootic counties, and they received lots of transfusions.

[Slide.]

What we tried to do very early on, then, is look at our organ donor to determine if this person had West Nile virus infection prior to the crash, and this is an exhaustive search by the Georgia and Florida state health departments, as well as CDC. All we came up with was 75 lambda of early serum. This is serum that was collected

prior to the first transfusion.

We were unable to demonstrate any antibody to West Nile virus in there. Our TaqMan was negative, and the culture, I put "culture pending," I am not sure that we had enough to culture, and if we did, I am not sure what it is going to mean.

Since that time, by the way, about two ago we identified a new vial of serum that had been collected by police in terms of the investigation of the crash, and those have been sent to Fort Collins, so hopefully, this slide will change in the coming weeks.

We then identified some late--it says serum, but it is actually plasma from the organ donor--and again, no antibody to West Nile, but now we had a very low level, but repeatable positive TaqMan for West Nile virus. This one, the culture is pending and it is still growing or it is not growing anything, but it is still incubating.

[Slide.]

You have to ask yourself, well, what about the transfusions. Here, the organ donor comes in, they are healthy, they are in a motor vehicle crash. There is no evidence that an encephalitis presentation contributed to that crash. In fact,

they received blood products from 63 unique donors. Those 63 donors actually produced about 142 co-components, and here is the breakdown.

I don't have to tell you how massive the investigation is. There are 63 organ donors or blood donors for the organ donor that are going to be approached. There is 35 recipients of the co-components. There is 27 of these units, however, being returned from the fractionator, but 2 have already been pooled by a fractionator. The other ones have been expired, broken, discarded, or simply not distributed.

[Slide.]

So, where are we in terms of the investigation? American Red Cross has been invaluable in terms of their contribution. They have located the segments from donation that we are currently testing in Fort Collins. They have identified and retrieved in-date co-components that we are testing in Fort Collins.

They are identifying the consignees that transfused the recipients of co-components. They are going to be identifying, and, in fact, they have already started identifying and contacting the donors, the blood donors to the organ donor, so

that we can obtain more information, as well as test them for IgM to West Nile virus.

They are assisting the state health departments, CDC, in terms of identifying the consignees, to do the same thing with recipients of potentially infect co-components. They, too, will be tested for West Nile virus IgM.

[Slide.]

So, the ongoing investigation then, what are we trying to do? We are trying to estimate the infection date of the organ donor. That is why we continue to look for tissues and liquid from the organ donor, because we are trying to figure out when this person was infected. So, we are continuing to test other tissue and blood.

We are currently doing TaqMan PCR of the segments from the original blood donors, as well as any recovered products. Then, of course, as I mentioned in the last slide, we are going to be determining if the donors were recently West Nile virus infected, and that will be by doing serology for IgM, and then the same with the recipients.

[Slide.]

This is my second to last slide. I apologize for going over.

This organ transplant very likely resulted--I added "very likely" because that is the way CDC is, we are a conservative group. I would like to say that organ transplant resulted in these four West Nile virus illnesses in terms of the organ recipients.

I don't think that that is going to be an arguable point. It is very unlikely that these four people were infected by mosquitoes and all came down with this illness, but we still have some more work to do to completely nail that down.

I want to emphasize that mosquito bites are still the principal means of acquiring infection in endemic and epidemic zones in this country, but that transfusion, when you look at this case, you have to consider it. We have to go out and we have to ask ourselves whether the transfusions were the source of infection to the organ donor especially when you look at some of these results.

But I think it is also fair to say that to date, there has been no case of West Nile virus infection that has been shown to be transfusion, and it still in there because that's the same thing I said week.

Next and last slide.

[Slide.]

We are involved in other investigations. In fact, yesterday, we were on a conference call with the state health departments, all 48 of the contiguous states, and we are soliciting more case reports from the state health departments, and what we are doing is looking for probable or confirmed cases of West Nile meningoencephalitis in persons who received blood products in the four weeks prior to their illness onset.

To date, we have been involved in investigations in Georgia, the one that I just described, as well as Mississippi, North Dakota, and Louisiana. So, right now we have about six ongoing investigations.

That is it. Do you want me to take questions or wait until Dr. Goodman is done?

DR. NELSON: Any questions? Harvey.

DR. KLEIN: Could I ask you if those handful of lab infections that you reported, were they from concentrated virus or were they from human specimens?

DR. MARFIN: It is a mix. In terms of the inhalation, it was from concentrated virus. In

terms of the percutaneous injury, it could be working with infected tissue directly taken at necropsy, or it could also be concentrated virus, as well.

DR. KOFF: I think you said we are halfway through the current epidemic. Can you give us some sense of what you would envision the total number of cases, and is this based on last year's experience?

DR. MARFIN: We can't base this year on any year's experience with West Nile. What we are looking to is the 1975 outbreak of St. Louis encephalitis in which a large number of the cases occurred in the last week of August and the first two weeks of September, and it primarily affected the Midwest.

The states at that time that were affected were Ohio, Illinois, Indiana, and those are the big three states. We are kind of seeing the same situation again this year. We are seeing Cleveland, we are seeing Chicago, we are seeing St. Louis, a very, very similar pattern. So, we are waiting for later reports meaning the September reports from these areas. In addition, there is always a lag with regards to surveillance data.

DR. SCHMIDT: I would like to see in the record something I consider a correction. In the transfusion literature, in the recent report from the CDC, it states that another flavivirus, dengue, was transmitted by transplantation in Puerto Rico in sort of a background information.

Well, that was 1995. Granted, the dengue laboratory for the CDC is in Puerto Rico, but at that time, I was the Director of Clinical Service for the American Red Cross in Puerto Rico, which supplied this particular hospital with all of its transfusion services and arranged through the Miami Red Cross to back up the bone marrow transplant.

The case was two sisters. The timing was right that after the transplant, both developed dengue, however, just before the transplant, both sisters' young children were at home, they shared a bedroom, and we heard about the urban Culex, well, there certainly are a lot of urban Culex in San Juan while I was there, and I remember specifically the admonition from the Health Department to be aware of the bedroom closet because that is where they were.

So, I think the evidence for this dengue transmission by transplantation was circumstantial,

and the significance only is that now it's in the transfusion literature as a fact.

DR. NELSON: I think it may be very difficult to separate this out to exclude mosquito transmission even in somebody who has been transfused, but even if you have a couple of donors positive, that still doesn't prove that it was transfusion, so it is a difficult problem, I think.

DR. MARFIN: I think you are correct. I think that what we would be looking for would be either demonstration of virus in the segment going into the organ donor in this case or you are identifying IgM-positive donors, and then you have potentially as many as three co-recipients--that is a situation we haven't identified--and then showing that they are all IgM-positive, as well. The likelihood of that would be low, but it is circumstantial.

With regards to the dengue, I have spoken about this with my division director Duane Gubler, who has been looking for evidence of a transfusion excluded from transplantation, evidence of dengue like for 30 years, and he brought up that case, but I had to point out to him that there is transplantation involved there, so it is not as

straightforward as we would like, but your point is very well taken.

It is very difficult to show for dengue and yellow fever, not necessarily because it doesn't happen, but because the infection rate in the population is so high, how do you ever attribute it to the transfusion as exposed to exposure.

DR. NELSON: But these organ transplants are pretty convincing at this point.

DR. FALLAT: Could you amplify a little bit more about the parallels of this epidemic with the St. Louis epidemic to give us some at least speculation about what the future holds?

DR. MARFIN: I can tell you that in 1974 through 1976, there were probably about 2,500 cases reported over that three-year time period, maybe a little more, but '75 was the big year, and the infection rates were, as I mentioned, highest in Illinois, Indiana, and Ohio. Those were the big three. A lot of cases were in Chicago. They came actually late in the year.

With regards to more about that, I mean it was very much like West Nile virus. It is predominantly older people who had West Nile virus

meningoencephalitis. During that time, there were no cases of transfusion-associated St. Louis encephalitis reported.

Did we have the technology to identify it, did we have the surveillance to identify it? Probably not. Do we have the capacity to go back and look at some of those things? It's a question that we are contemplating, but I don't think that we have any of the material left.

DR. FALLAT: I was thinking more in terms of what has happened since 1975 with regard to the St. Louis virus, and would you speculate that the same thing is going to occur with the West Nile virus.

DR. MARFIN: Oh, I am sorry. In fact, 1975 was a banner year and most of the country responded by intensifying the control of their urban Culex, and there were huge programs put into the control of urban Culex.

As things will happen when diseases don't show up for a number of years, those funds for the control of urban Culex begin to dwindle, and, in fact, as we have come into this year and last year, that is what we have seen. We have seen large urban areas that used to have good mosquito control

operations, they longer have those, they are not longer there.

Has that contributed to the outbreak of West Nile virus now? There will be some people that would suggest that. Since 1975, there have been some outbreaks. In 1989, in Mesa County, Colorado, in Grand Junction, there was an outbreak. In 1991, in Pine Bluff, Arkansas, there was an outbreak. Last year in Northeast Louisiana, there were 72 cases of St. Louis encephalitis in Northeast Louisiana.

So, it is still out there, and you can see that the pattern is somewhat different. It is hitting, burning, hitting, burning, hitting, burning, and you are not seeing the persistence as we are in some of these areas, and you are seeing very focal outbreaks. There is no large tracts of area that are involved in the epidemic as they were in 1975.

Why is that? I think that it is probably because this virus is coming into equilibrium with its mosquito vectors, it is coming into equilibrium with its amplifying hosts, and whether it gives us a St. Louis encephalitis-like pattern or whether it is going to forge its own pattern is simply not

known, and we don't enough data yet.

DR. LEW: Although it sounds like your CDC is asking for people to think of cases of people who get illnesses after four weeks, number one is why was four weeks chosen. I would assume that those who got the virus potentially from transplant had disease soon after, but if you could also elaborate on that, when did they have to start their illness.

Also, I guess if the illness does come within four weeks--is that what you are saying?

DR. MARFIN: Within four weeks of transfusion, yes.

DR. LEW: But what data is that based on?

DR. MARFIN: Oh, the data. It is going back and looking at the organ transplants. Some of these people had illness onset as long as 19 days after the organ transplantation. I would have to go back and look at my line listing, but that is why there is always a consideration, did they get infected while they were out of the hospital during those 19 days.

But, in fact, if you look at them, they tend to be a little bit longer. I think, like you, a lot of us would have said these people have no

intact immune system, why do we not have onset of illness by the second day or the third day, and, in fact, that was not seen. It would appear to be a little bit longer although I think one of the cases was within about four or five days.

When you go back and you look at the 1957 data in which people with terminal cancer were given West Nile virus experimentally, you do see people who had viremia the very next day after they were injected intradermally with West Nile virus. In fact, those would be the higher levels of viremia that we have seen, but, in fact, illness came on, on the second or third day.

So, that is a little bit of a difference here. These are organ transplants. Why is there that delay, and we do not know why, but that is why are we pushing out those dates. We now know that some people can become ill as long as 17 to 19 days out after infection.

DR. LEW: One last question. Is that the only prospective study that you are reaching out to do, to look at possible transmission of West Nile?

DR. MARFIN: I am sorry. Which study?

DR. LEW: Well, it sounds like CDC is asking people to consider this and then refer it to

you guys, but is there any other prospective study, or maybe the blood banks know, to try to take a look at that issue?

DR. MARFIN: We do have a surveillance system in this country that is one of the CDC's few real-time surveillance system. It is called Arbonet, and Arbonet collects cases within days of their identification, and we are adding a new component to that, to specifically inquire of states and ill persons about transfusions, so those will also result in the potential identification of new cases.

DR. LAAL: What is the Israeli experience with the West Nile virus to blood transfusions?

DR. MARFIN: I am sorry, I don't know, but it is one of the things that is on our list of things to do. Last year they had hundreds of cases in Israel, as well as the year before. They have a very similar age structure to ours, they have a very similar medical system, but it is something that we are going to reach out and find out what their experience is.

DR. FITZPATRICK: I am sorry, I might have missed it on one of your slides, but have you been able to get tissue samples from the organs and test

any tissue samples from the organs that were transplanted?

DR. MARFIN: The organs that were transplanted, yes. Some services will set up a routine biopsy as part of their postoperative care. Some will only do it when there is evidence of rejection. We have looked at, at least one of the kidneys, and we were unable to demonstrate any viral antigen in that kidney.

Thank you.

DR. NELSON: Dr. Goodman from FDA.

Jesse Goodman, M.D.

DR. GOODMAN: Good morning. Similar to Tony, I have to apologize for those who heard my presentation at the PHS Advisory Committee last week, but similar to him, I can say it is updated and I hope you find it interesting.

I was going to say that it is not quite as dramatic, but perhaps in our case we have the regulators falling from the trees right now, at least that is how we feel late at night when we are working on this.

[Slide.]

Here is some background. Basically, the world of thinking about West Nile virus in blood

changed on 9-4. Before that time, we were all concerned about the biological plausibility for transfusion transmission to occur, and this was based on the known transient viremia in West Nile virus patients, as Tony showed you, believed to be on the order of just days to perhaps a couple of weeks, the fact that most patients with infection are asymptomatic and therefore would certainly be at risk of being in a donor pool.

The risk, though, was viewed as likely to be quite low. Why is that? Well, there is certainly on chronic carrier state known, and again, as Tony reported, some fairly extensive and systematic and also diagnostic studies from CDC reported pretty low yield of PCR in cultures in patients with West Nile disease. That would certainly suggest that once infected, you don't have prolonged viremia, even as detectable by a sensitive PCR assay.

There have been no cases reported in prior years or in endemic countries. I didn't get the details of the question about Israel, but FDA did make at least an informal query to Israel, and the Israeli blood folks could not tell us about any cases of transfusion transmitted disease there.

One point I would like to make about that is that, you know, just like the healthy public exposed to West Nile, it is possible that there could be transmission through transfusion and that many or most transfusion recipients would not have disease, but we need to bear that in mind, that the absence of evidence in other countries that this was not transmitted, the absence of evidence of transmission is, of course, not proof that transmission did not occur.

CDC recently published some risk modeling based on the 1999 New York epidemic and an assumed six-day viremia and 100 percent transmission rate, and came up with an estimate that something like 1 to 2 in 10,000 individuals during an epidemic could conceivably be viremic at one time when they were in a donor pool.

That is a useful estimate, but it is based on a number of assumptions and another epidemic.

With plasma derivatives, we do know that closely related flaviviruses, which have been used in most of the inactivation schemes, these include enveloped viruses, such as BVDV, hepatitis C, et cetera, are very inactivated, but this situation is being looked at carefully I know by the plasma

industry. Even though we are confident of this, it may be that other studies will be done.

So, based on the above, FDA, working together with CDC and NIH, did issue the alert 8-17 about this possibility, trying to raise awareness and particularly in endemic areas or epidemic transmission areas be sure to be very vigilant about donor exclusion criteria, such as fever and prodromal symptoms.

[Slide.]

What about after 9-4? Well, that is the day when based on confirmation of diagnosis in multiple organ recipients and evidence that the donor may have been infected, we concluded there was a high likelihood that transmission has occurred via transplantation, as CDC just presented.

As mentioned, the possible sources still remain natural mosquito-borne exposure or the multiple transfusions which this donor received. Given the number of multiple transfusions, a very high number, we are quite concerned that that could be a source in this case although there obviously are alternative explanations.

So, there has been a heightened level of

attention and concern. At present, though, there is still no proven transmission by transfusion, there is an increased suspicion with additional recent reports and some suggestive PCR results, which Tony didn't go into, but I believe are mentioned in an NMWR that is out or forthcoming.

But this is a very incomplete investigation and ongoing at this point, and cultures, follow-up serology of these individuals is pending. In some of those instances, results are negative, as well.

I think it is important to recognize and some of the questioning in this room before with Tony raised this, that the results of these particular few case investigations may, in fact, not be definitive. They may be or they may not, because individuals in areas with exposure to blood from potentially viremic donors have so far also had high potential for naturally acquired infection.

So, follow-up serologies and PCR on any PCR-positive donors may be helpful in sorting this out, also, co-recipient tracking. Certainly, if one saw, as in the organ transplant case, a high number or co-recipients of products also developing

disease in a similar time frame, this would be highly suggestive, so we want to be vigilant to that, and hopefully, CDC's increased awareness in reporting mechanisms could bring that to attention.

In addition, if there were cases where there was long-term hospitalization prior to onset without mosquitoes flying around hospitals and having worked in many hospitals in the United States, I would say that mosquitoes do fly around hospitals, sometimes even bats and squirrels fly around hospitals, but this would seem helpful and unlikely.

Another thing would, and it is hidden by the button, but an out-of-area case. I mean I think if we had an instance where blood from a highly epidemic area was routed to an individual who had been in an area with no ongoing transmission, and that individual developed disease, that would be the kind of thing that would make us all feel pretty strongly that this was likely going on.

I think still getting back to the original point, it is biologically plausible, and I think I would be somewhat startled if this never occurred. The question is how often may this occur, is it a

problem, and what would we need to do about it.

[Slide.]

So, what has been the public health response so far? You heard much of this from Tony. There has been a very close working relationship, very positive, between FDA, CDC, the States, the blood collectors in industry, and in the case of the organ transplant, HRSA, who regulates that area.

You heard about the continued investigation. There has been withdrawal of all in-date products as soon as CDC and FDA were notified of these cases. There has been a lot of work, such as this, with you, but also with the blood community, the media, consumers, to share information, and I think this can be challenging because sometimes information can be difficult, especially complex information like this can be difficult to communicate effectively.

On the other hand, I think the fact that we are sharing information helps increase trust and confidence and understanding.

Also, this stimulates reporting that we want to do. It gives us the opportunity to try to do balanced-risk communication that keeps in mind

the risk and benefits of transfusion and transplantation.

I think we need to continually give the message that there is uncertainty of the current knowledge base regarding risk, and this is rapidly evolving. Tony and our other colleagues at CDC, I mean we are being spun like a yo-yo by lab results and reports coming left and right, and we need to keep equilibrium and a careful look at those, and things may change in a matter of hours, days, weeks, or they may not.

It is still a very important point, and Jim Hughes of CDC made this, and I am sure Tony would agree, that the risk of West Nile virus from a mosquito bite right now is the big public health problem in this country. Of course, we are concerned about the safety of the blood supply, we are very serious about this, but that is another perspective.

[Slide.]

So, what is needed? Well, I think one of the questions that I heard before raised the question of how are we going to figure this out.

I think to some degree these cases may help, particularly if we have some definitive ones,

such as I suggested, but we do need to define the problem and rapidly deploy a research agenda, that retrospective studies are generally case reports and investigations, such as you have heard described, and others that may occur.

But also there is a potential to use some of the banked studies from some of the transfusion study groups and a group of people involved with that, and the FDA and CDC had a phone conversation yesterday about trying to mobilize such a study with one of the banked groups that may have sites in epidemic areas.

There is a need for prospective studies, we think, and a real important question particularly raised by some of the most recent testing data is that you saw the risk estimate from the original CDC study of Dr. Peterson based on the New York epidemic. It really predicted a very, very low incidence of viremia at a specific time in a donor population.

I think we need to be sure that we are not, based on some of what we are seeing and our level of concern, that there isn't something completely different and unexpected going on, and so we are trying to work with various partners to

mobilize a pretty rapid study during this season while transmission is still going on of the incidence of viremia in donors in an epidemic setting.

An early study may not be a definitive one, but it may give us a better idea of the scope, if any, of the problem. This should include emerging hot spots and also we think controlled populations where there is no disease transmission particularly given issues that come up about PCR methodologies.

Seroprevalence in frequently transfused individuals could be another study, studies to evaluate duration of viremia, et cetera, potentially needed laboratory research on the nature of the pathogen itself, its inactivation by various measures and conditions.

[Slide.]

Well, if we are identifying a significant problem, right now we don't know the seriousness or extent of it. As I said, we really believe we need to take this very seriously, and we want to prepare and move on these studies and on other things as if there were a problem. We can always then, if there is not one, at least have been ready, and if there

is one, be ready as quickly as possible.

So, it further intervention is needed, the basic arms of such an intervention could include the traditional donor screening and deferrals, and we have been asked questions at press conferences about could you exclude everybody with mosquito bites, et cetera.

Obviously, this would not be a particularly sensitive or specific intervention. We suspect that lots of people who maybe do not recall mosquito bites could be infected, and certainly the vast majority of people we know from the epidemiology, everyone in these areas is bitten by mosquitoes, yet, you saw seroprevalence data of 2 percent in some of these outbreak situations.

So, it wouldn't be effective and given current problems we heard about earlier today with supply, it could harm a lot more people than it could potentially even help even if this were a true threat in the blood supply.

It is possible that one could hone this if our CDC and State colleagues could identify sort of hyperepidemic areas, and if those seem to be the places where this risk were occurring, it is possible that one could try to, as a temporary

measure, remove donors from those areas if this were an emergency and the risk was identified and present and threatening lives.

If that occurred, there would be supply implications, as well, but I think again we would have to understand that we were dealing with a potential public health emergency. So, this is just something to look at.

Again, I would like to say none of this is FDA or CDC policy or recommendations. We are still in the early stages of an investigation to determine what is going on, but we are concerned.

You heard earlier from Jaro that there was a recent workshop. There is a lot of very innovative work going on in industry about pathogen inactivation. This is an area where there may be targeted products or targeted recipients or targeted areas that could potentially evidence a favorable risk-benefit ratio for considering those kinds of interventions under the right circumstances.

So, it is just something that we all need to recognize that although currently unlicensed, it is a potential part of our armamentarium.

[Slide.]

Well, a lot of questions raised about testing of donor blood if it were needed, and if it were needed, we would have to ask who needs it, should this be general screening of all blood versus should it be possibly targeted screening if we can identify high-risk transfusion recipients, or at-risk areas in terms of the donor pool, or defined time periods which we heard are rapidly expanding.

Antibody testing appears to be unlikely to identify most early asymptomatic donors with viremia, but whether, for instance, hypersensitive IgM assays might detect some, we just don't know that at this point.

It would appear that direct detection is--it is funny, this reminded me when I have been thinking about it, it is also the reverse of the HIV situation where the window period is where most transmission is going on, and there sort of is no other period, so our focus here is really on a window period--direct detection therefore would be most likely of potential value.

Of course, there is nucleic acid amplification, as Tony has described, this can be quite sensitive, although we need to say that the

levels of virus in blood appear quite low and one questionable issue is whether this would be sensitive enough to do on pooled specimens, such as done with NAT for HIV and hep-C. Antigen detection methods have been developed, but are significantly less sensitive.

These assays have really been deployed and developed in research and clinical lab settings. They have not been applied to samples where you would expect the overwhelming majority of samples to be negative and from healthy donors, and so their performance in that setting is unknown at this time.

So, there are challenges in terms of transferring research and academic and public health lab technology to an industry blood banking setting, the issue of validation and use for donor screening in low prevalence populations. These things can't be underemphasized.

There is many things that are wonderful in one center or one lab, that when the rubber meets the road, there are bumps, but on the much more positive side, and I have tried to say that I think if we have a problem here, you know, this country and our industries and our scientists have the

capability to respond to this.

It may not be overnight, but there are facilitating factors, one of which is all the industry, blood bank, and FDA experience with existing NAT testing. Those platforms are out there, the testing centers are out there, et cetera.

Another is that some of these diagnostic technologies currently in use, I think would be promising for adaptation into that, and that might speed availability again at least in targeted areas potentially under IND, et cetera, again, if this were needed.

[Slide.]

In finishing, the investigation continues. I think we should not underestimate the level of alert and level of concern we all have. Even though the risk has been believed to be quite low, I think we need to be sure that we work hard to be sure of that and to define it.

We do need to better define that risk, as I said, and strategies potentially to mitigate it. There has been really close interagency collaboration and the blood industry has been extremely cooperative.

There has been good communication and information sharing with multiple parties and again I think that there has been a balanced yet flexible perspective on the level of risk, but it is a real challenge to keep doing this with rapidly evolving, almost on a daily basis, and an uncertain situation, and sometimes scientists and public health people and regulators, we just have to I think be candid and share the information and try to explain the complexities of it, but, you know, that is life.

FDA, we are certainly considering the need to move towards guidance for industry, and I think we are going to be planning to move in that direction rapidly, but again, given the changing target here, we want to be able to adapt to that in terms of what the guidance is.

For now, we have been involved with CDC and others in communication with industry that has encountered these cases or questions related to West Nile, to try to be helpful and consistent in those communications, and we welcome that.

If there is a potential need for a donor screening test, and I would say there certainly is a potential need at this point, we feel it is

important to be as ahead of the curve as possible and encourage and facilitate technology development and transfer.

I would say that is probably true given what has gone on this year with the expansion of this epidemic. This may not go away, and that even if we don't have a big blood problem this year, we should at least have the things in place, so that if one were to develop, we could deal with it.

To that end, we are planning and working with both the blood community and the medical diagnostic device industry to try to bring people together to begin to move forward on these issues there.

That is really about it. In terms of the BPAC, we welcome discussion here, we welcome input, and I know that FDA and CDC will continue to seek that input.

Thank you very much.

DR. NELSON: Thank you.

Yes, Judy.

DR. LEW: Could you help put this, or maybe CDC, as well, in perspective in terms of we heard that maybe 100,000 people have been infected, how does this compare to St. Louis eastern equine,

western equine?

I mean these are diseases we expect to see during the summer, so if it is truly epidemic of West Nile, I mean in comparison to the other encephalitides, which we normally would test for if we saw encephalitis.

DR. GOODMAN: Maybe Tony can answer, but this is an epidemic in this country at this point, and there are less cases of these other diseases right now.

Do you want to comment?

DR. MARFIN: Just to reiterate what Jesse said, if we looked at last year, we are talking about potentially 900 to 1,000 total infected people for the entire year, so this is out of proportion to previous years.

Theoretically, it should be about the same as St. Louis encephalitis, in fact, the ratio is about the same. It is about 1, in that case, it is a little higher, 200 to 300, and the patterns, the viremias, all of the things are almost identical. It is almost the same virus. With regards to eastern, in fact, it does have a higher attack rate, so it would be a relatively small number.

The fact of the matter is, though, that we

are not seeing most of those. We have not seen western equine encephalitis in this country for many years. Every year, there are 100 to 150 cases of La Cross encephalitis, but that primarily affects younger people, 9-year-olds, 10-year-olds, that are not donating.

So, in terms of arboviruses, this is a brand-new phenomenon given what has been going on with the others for the past few years.

DR. LEW: I recognize for West Nile, since it is new to this country, this is truly an epidemic, but just in terms of perspective, we are talking about we are worried about West Nile in our blood system, whatever, but St. Louis has been around and every year it infects so many people.

So, comparatively, is it just meeting what St. Louis has always been at its baseline, not epidemic, or is this really much more than even St. Louis at this time. Do you see where I am going with this?

DR. MARFIN: Well, I can say that we have had epidemics in the past 25 years of St. Louis encephalitis. Last year, there were 72 cases in one city in Louisiana. There were no other cases in the country or one or two.

That is the pattern that they have established. It is very focal. It is periodic. The last one before last year was 1991, so we haven't had an outbreak of St. Louis encephalitis, a focal outbreak, in 10 years. So, it is very, very spotty.

I don't know whether West Nile virus is going to become like that. I just know that this year we have a lot more cases than we would have anticipated.

DR. GOODMAN: I think a legitimate comment and maybe where you were coming from is there are probably other viral diseases that cause transient viremia and offer the theoretical possibility of transmission in blood, and we just need to keep this in perspective with other risks and other infections.

But we are dealing here with this striking transplant case and with some reports of at least cases potentially associated with, but not clearly due to, transfusion. So, I think we do have to keep that in perspective, that is different, and obviously, there is much more influenza, and influenza can be in your blood for a short time.

We are not aware of horrendous problems

with influenza such as this, but again, how robust are our studies and monitoring systems to detect that. So, in a way we have a challenge here. I mean it is a modeling for many things. It is a model for dealing with a new potential threat to blood, but it is a model also to keep that in perspective and try to respond to it responsibly and with changing and grossly deficient knowledge.

DR. NELSON: I think this epidemic sort of illustrates that there are many different agents that come and go, and this year West Nile is very important. It would be good if there were sort of an ongoing pre- and post-transfusion serum bank linked to donors that we could look at risks, and there were in the past, the TTV study, the FACT study, et cetera.

As far as I am aware, there is no ongoing large, I mean NIH has some follow-up, but in terms of a comprehensive database that we could go look at a new risk, I don't think there is one. It is often hard to make a case that, well, something is going to happen and we need to know it. It is always retrospectively, after it happens, and then you can't get the data that you really need.

During the FACT study, we studied several

different agents sequentially, not what we started with, but it is has always been difficult to get that funding, but it would be good if we had a donor-linked pre- and post-transfusion that we could look at, because with most infections being asymptomatic, both in the donor and the recipient, you are really looking at a really small iceberg when you are looking at clinical events retrospectively.

DR. GOODMAN: Right, and I think some of the repositories--again, Jay and many of you at the table know much more about this than I do--but some of the repositories like REDS, RADAR, et cetera, are potential resources for looking at this.

DR. HARVATH: Ken, I would like to say that the NHLBI REDS study has the RADAR repository, and I think Mike Busch would like to describe what the discussions have recently been about utilizing that.

DR. BUSCH: Yes, the RADAR repository is being put down by REDS. It is actually a collaboratively supported study with CDC. There are five large blood centers, main REDS centers, plus two CDC-supported sites that are currently freezing down donation samples pre-transfusion, and

then follow-up samples from recipients. I think the total goal is about 10,000 recipients, about 50- to 100,000 units that went into those recipients plus additional donations that didn't go into the recipients are being frozen down in parallel.

These include some of the hot spots. Detroit is one, and, in fact, will likely include Detroit in an initial study of West Nile prevalence. There is also a study at NIH that is called the TRIP study, that Harvey Alter is conducting. It is kind of interleaved with the RADAR, it has got more frequent recipient sampling.

In this particular epidemic, it is turning out are the sites where we are recruiting these donors and recipients at the hot bed of the epidemic, and so we are realizing that we need to supplement what we are going to do with RADAR with some unlinked and then downstream linked studies in some of the other hot zone regions.

MR. RICE: Just a clarification. With respect to an identified donor that went into a manufactured pool, the current way that that is being handled is a withdrawal situation of in-dated product as opposed to a recall, and has there been

any established like effectiveness check as follow-up since you are taking the product out of circulation as a result of an identified donor post-manufacture, is that the way that it is currently being handled as opposed to a more formal situation in a recall sense?

DR. GOODMAN: I will let Jay comment, but in the absence of guidance, which as I said we are working towards, that is the way it is being handled, but FDA has been involved very directly in each of these cases with the blood organizations.

Jay, any comment on that?

DR. EPSTEIN: Yes. We have not been recommending withdrawal of pooled products, in other words, there have been no plasma derivatives withdrawals.

At the present time, however, it is also the case that we have not been told of a product that contained a unit made from a donor who potentially may have transmitted to a component recipient, but our current perspective is that we have reviewed all of the validation data for virus inactivation of the plasma derivatives. In all cases, representative viruses in the Flavivirus family were studied, so we believe that the

products will remove or inactivate, and the processing will remove or inactivate this flavivirus.

We have a dialogue ongoing with the fractionators to talk about additional studies with the West Nile virus, but bear in mind that these products have been made safe for hepatitis C and that all of that was done with marker virus studies since you can't grow hepatitis C in vitro.

So, we do think that the safety profile is very good, and we are not at this point in time asking for derivative withdrawals. What we have bee doing case by case is discussing with the blood centers retrieving any in-date components from the donors when the donors are under investigation for the possibility of having transmitted through components to a recipient.

DR. GOODMAN: And we are asking for retrieval of any plasma that has gone to fractionators, as well.

DR. EPSTEIN: Right.

MR. RICE: So, you are retrieving the components, but not the derivative products.

DR. EPSTEIN: That is correct.

MR. RICE: Okay.

DR. NELSON: Other comments?

Thanks, Dr. Goodman.

DR. GOODMAN: Thank you.

DR. NELSON: The next item is a discussion of Self-Administration of the Uniform Donor History Questionnaire for First-Time Donors.

Dr. Alan Williams.

It has been suggested that maybe since there are several presentations, we are a bit behind, maybe we should take a break and do it afterwards, and then up until the lunch hour, we will discuss the whole issue rather than have one or two presentations and then a break.

DR. WILLIAMS: It sounds fine particularly since those aren't my slides.

[Laughter.]

DR. NELSON: We will come back at 10:30, please.

[Break.]

DR. NELSON: Dr. Williams.

Self-Administration of the Uniform Donor History Questionnaire: First-Time Donors

Background and Introduction

Alan Williams, Ph.D.

DR. WILLIAMS: Again, good morning. I

would like to start off with just a brief administrative announcement before getting to the topic.

As many of you know, blood establishment registration, which is for blood and plasma collection establishments and all FDA-registered laboratories, is required annually near the end of the year.

We would just like to provide a heads-up that it is FDA's intent this year to offer an electronic version of this registration form. This form is actually going to mimic the paper form and will be available with last year's data and can simply be modified electronically and resubmitted.

The detailed information about this and the instructions for completion will be sent to all registrants at the time of renewal, and acknowledgment of receipt of the form will still be done manually just to ensure that everyone knows that the material has been received. So, just an indication of FDA's intent in this direction.

[Slide.]

The major topic for discussion is a follow-up to previous discussions regarding the revised Uniform Donor History Questionnaire which

has been under active study by an interagency task force coordinated by the American Association of Blood Banks, and the decision point for today really concerns whether components of the questionnaire should be self-administered versus administered by oral interview or equivalent means.

[Slide.]

I would like to start of the discussion just by establishing a little bit of context as far as regulatory oversight of the mode of administration of the donor screening process as opposed to the content of the screening process.

Prior to the early 1990s, there was really no regulatory position on donor screening methodology and industry practices tended to be mixed, varying between self-administration of certain portions of the questionnaire to actual interview administration of the whole or portions of the questionnaire.

That changed in early 1992 with an FDA memorandum recommending direct oral administration of the AIDS-related high-risk questions, and this was on the heels of a published study by Donna Mayo, et al., in Transfusion, showing that, in fact, this method was more effective at eliciting

high-risk behaviors from the donor population.

In 1998, based on submitted data, which to my knowledge have not been published, some blood centers applied and have been approved for a fully self-administered questionnaire, and that includes the higher risk questions. This is not true of the entire industry, it is limited to a subset of current blood establishments.

In January of 2002, final guidance was issued with respect to the travel deferrals for protection against variant CJD and BSE exposure. This guidance recommends oral questions about European travel and residents for first-time donors.

The reason for this change was specific to the nature of the questions and the complexity of the information that was being gathered. From the earlier guidance relating to UK travel, there was recognized a marked increase of biologic product deviation reports to FDA related to post-donation information.

In Fiscal Year 01, 76-plus percent of the deviation reports were related to post-donation information or PDI, and close to 90 percent of the PDIs were due to false negative screening tests,

that is, the donor was apparently aware of the information at the time of donation and it wasn't reported as part of the screen.

Interestingly, about 45 percent of those PDIs were related to either United Kingdom or malaria travel questioning, and these data are available on the FDA web site.

In April of 2002, pertinent to today's discussion, FDA issued its current thinking on self-administration of the donor questionnaire in draft guidance, and I will go over some elements of this guidance document because they impact on the revised Uniform Donor History Questionnaire and its future mode of implementation.

Some key aspects of this guidance document were recommendation for oral interview of first-time donors, and the intent of the guidance was to apply this to the newer, more complex travel questions, as well as questions that use more complex medical or scientific terminology, such as Chagas disease, babesiosis, xenotransplantation, and terms like that, as well as the high-risk questions.

This guidance actually removes the recommendation in the earlier memo for oral risk

interview for the high-risk questions and repeat donors, and the intent, although this is discussable based on the considerations being given to the parameters today, that previous approvals for oral questioning with respect to other aspects of the questionnaires will stand. In the absence of data showing any sort of safety problem, FDA doesn't currently feel that mode of administrations that are currently approved should be altered.

[Slide.]

A little more specific history with respect to the discussions of this committee particularly at the last meeting, we gave a little background of certain aspects of the donor qualification process that we didn't want to spend time reviewing today, that is, the importance of having an accurate donor qualification process not only to remove risk for agents such as HIV and hepatitis C where there are tests available, but equally, if not more importantly, to have the ability to remove potentially harmful donors in situations where a test does not exist. So, accuracy is very important.

Secondly, we reviewed the stages of donor qualification. This runs the gamut from

pre-donation education of the donor and self-deferral at that point, to screening and self-deferral at the time of the donation process, to recognition after the donation fact and reporting by post-donation reports.

We reviewed the donor screening process, evidence of successes, namely, that first-time donors and repeat donors have considerably lower levels of risk in evidence compared to the general population, and some of the areas where sensitivity of the process appears to be flawed, for instance, those donors who are found to have a transmissible infection at the time of screening frequently have risks that should have prevented their donation.

Survey research shows that a certain proportion of uninfected donors also carry risk.

I think I would also attribute the post-donation information data as representing a failure of that donor to recognize that that information should have been brought forward at the time of the screening process.

Unfortunately, most of these data cannot be stratified in terms of whether the donation screening process was done by a self-administration process or by an oral interview. The data for the