UNITED STATES FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP

IDENTIFICATION AND CHARACTERIZATION OF INFECTIOUS DISEASE RISKS OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

College Park, Maryland

Wednesday, February 8, 2017

PARTICIPANTS:

Welcome/Opening Remarks:

WILSON BRYAN, M.D.
Food and Drug Administration

SESSION I: Estimating Magnitude of Emerging Infectious Diseases:

MICHAEL STRONG, Ph.D., Moderator
StrongSolutions

Emerging infectious diseases in the U.S.:

BOB BOLLINGER, M.D.
Johns Hopkins University

Predicting the potential impact of an emerging infectious disease on public health:

MARK ROBERTS, M.D.
University of Pittsburgh

Estimating disease incidence/prevalence in general and donor populations:

BRAD BIGGERSTAFF, Ph.D.
Centers for Disease Control and Prevention

Estimating disease incidence/prevalence in the HCT/P donor population:

DON BRAMBILLA, Ph.D.
RTI International

Panel Discussion:

BOB BOLLINGER, M.D.
Johns Hopkins University

MARK ROBERTS, M.D.
University of Pittsburgh

PARTICIPANTS (CONT'D):

BRAD BIGGERSTAFF, Ph.D.
Centers for Disease Control and Prevention

DON BRAMBILLA, Ph.D.
RTI International

SESSION II: Potential for Donor-Derived Infectious Disease Transmission by HCT/Ps:

MATT KUEHNERT, M.D., Moderator
Centers for Disease Control and Prevention

History of infectious disease transmissions by human cells and tissues:

MATT KUEHNERT, M.D.
Centers for Disease Control and Prevention

Infectious disease transmissions by conventional tissues:

TED EASTLUND, M.D.
University of New Mexico School of Medicine

Infectious disease transmissions by ocular tissues:

MARIAN MACSAI, M.D.
NorthShore University HealthSystem

Infectious disease transmissions by HPCs:

JOHN MILLER, M.D., Ph.D.
National Marrow Donor Program

Infectious disease transmission by reproductive cells and tissues:

DEBORAH ANDERSON, Ph.D.
Boston University

PARTICIPANTS (CONT'D):

Relevant communicable disease agents and diseases:

BRYCHAN CLARK, M.D.
Food and Drug Administration

Panel Discussion:

MATT KUEHNERT, M.D.
Centers for Disease Control and Prevention

TED EASTLUND, M.D.
University of New Mexico School of Medicine

MARIAN MACSAI, M.D.
NorthShore University HealthSystem

JOHN MILLER, M.D., Ph.D.
National Marrow Donor Program

DEBORAH ANDERSON, Ph.D.
Boston University

BRYCHAN CLARK, M.D.
Food and Drug Administration

SESSION III: Challenges of Traditional Screening and Testing Approaches for Donors of HCT/Ps:

JAY FISHMAN, M.D., Moderator
Massachusetts General Hospital/Harvard Medical School

Current approaches for HCT/P donor screening and testing:

MICHELLE McCLURE, Ph.D.
Food and Drug Administration

Screening and testing of HCT/P donors:

PARTICIPANTS (CONT'D):

DAVID GOCKE, M.D.
Musculoskeletal Transplant Foundation

JENNIFER LI, M.D.
University of California Davis Eye Center

Test performance when using post-mortem blood:

HARRY PRINCE, Ph.D.
VRL-Eurofins

Pathogen persistence and infectivity in cells and tissues: Zika virus:

GRAHAM SIMMONS, Ph.D.
Blood Systems Research Institute

Panel Discussion:

MICHELLE McCLURE, Ph.D.
Food and Drug Administration

DAVID GOCKE, M.D.
Musculoskeletal Transplant Foundation

JENNIFER LI, M.D.
University of California Davis Eye Center

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REGISTRANTS:

ROBERT ALLISON

BOB ALBRECHT

RACHAEL ANATOL

REGISTRANTS (CONT'D):

SHARON ANDERSON

JUDITH ARCIDIACONO

JOHN ARNONE

MONA ATKINSON

REGINA BAKER

MICHAEL BAUER

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KIMBERLY BENTON

JAMES BERGER

BRAD BLANEY

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SCOTT BRUBAKER

JENNIFER WHEELER BUENGER

COREY BURKE

MICHELE CARROLL

JEFFREY CARTMELL

KINNERA CHADA

DAVID CHO

SHANA CHRISTRUP

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REGISTRANTS (CONT'D):

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JOHN COVER

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MELODY EBLE

ANNE EDER

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EMMANOUEL FATTAHI

REGISTRANTS (CONT'D):

DONALD FINK

ANDREA FISCHER

MAGALI FONTAINE

RICHARD FORSHEE

STEPHANIE FOX-RAWLINGS

MARK FRIEDMAN

MARK GARCIA

MAYRA GARCIA

CALLIE GIBSON

SUE GITLIN

TARA GOODIN

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SARAH GRAY

GLENN GREENLEAF

MELISSA GREENWALD

DEBORAH GRIFFIN

MARC GURWITH

JOYCE HAGER

BRANT HAMEL

MARGARET HARPER

MEGAN HARRINGTON

REGISTRANTS (CONT'D):

CARRIE HARTILL

PING HE

ELLEN HECK

PATRICK HANLEY

HEATHER HILL

CHAK-SUM HO

MICHAEL HOULE

DEBORAH HURSH

LAARNI IBENANA

KAVITA IMRIT-THOMAS

PAWAN JAIN

TERRI JAMISON

ABE JANIS

BETSY JETT

AUDREY JIA

AMANDEEP KAHLON

NAYNESH KAMANI

SAFA KARANDISH

KRISHNA MOHAN KETHA

ANITA KHAN

BENJAMIN KIBALO

REGISTRANTS (CONT'D):

YEOWON KIM

RICHARD KOLOVICH

MUKESH KUMAR

MEGHAN LAMBERT

MICHELLE LEWIS

MINGMING LI

DARYL LIRMAN

SHYH-CHING LO

KATHY LOPER

CATHY LOPEZ

JASON LoVERDI

SANDRA MAGERA

BABITA MAHAJAN

JENNIFER MAHONEY

NORM MARCUS

IRIS MARKLEIN

CHRISTINA MARKUS

NANCY MASSONI

BARBARA MATTHEWS

CHRISTINA MAYER

KOHAR MAZMANIAN

REGISTRANTS (CONT'D):

QUINN McCARTHY

KEVIN McDORMAN

RICHARD McFARLAND

BARBARA McGOVERN

JUAN MERAYO-RODRIGUEZ

ANDRA MILLER

KEN MILLER

BENJAMIN MINTZ

SHEILA MORAN

MATT MORTENSEN

NAIM MOSES

HASSAN NAGY

HIRA NAKHASI

WILLIS NAVARRO

BRIAN NILAND

KATERYNA ODARCHENKO

STEVEN OH

JOEL OSBORNE

IHAD OTHMAN

MARC PABLO

REGISTRANTS (CONT'D):

JANAK PADIA

BRYAN PARKER

LISA PATE

LINDA PELTIER

ELIZABETH PHELAN

ABIGAIL PHIPPS

SIMONE PORTER

RAJ PURI

MERCY QUAGRAINE

MICHAEL REAL

SHANNON RENAUD

PAUL RICHARDS

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VANESSA RODRIGUEZ

MARK ROGERS

JUAN ROJAS

ASHLEY RUIZ

MARTIN RUTA

MOHAN KUMAR HALEYUR GIRI

TAL SALZ

JENNIFER SCHARPF

REGISTRANTS (CONT'D):

DANIEL SCHULTZ

JOSEPH SCHWARTZ

DEBBIE SEEM

NAWRAZ SHAWIR

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CHUN-PYN SHEN

KILEEN SHIER

ALEX SMITH

BLAKE SMITH

DAVID SMITH

ROBERT SOKOLIC

YOUNGME SONG

JASON ST. PIERRE

JEAN STANTON

LEAH STONE

CHRISTOPHER TALBOT

WILLIAM TENTE

RAJESH THANGAPAZHAN

SHERYL TRAN

JILL URBAN

MICHAEL URICH

REGISTRANTS (CONT'D):

QUYNK VANTU

KERRI WACHTER

DONGYAN (TOM) WANG

MARIA WEISER

MARTHA WELLS

AMITTHA WICKREMA

PAMELA WILLIAMS

RYAN WILLIAMS

CAROLYN WILSON

FRANK WILTON

JEANNINE WITMYER

CELIA WITTEN

PATRICK WOOD

HONG YANG

JESSICA YOZWIAK

JAN ZAJDOWICZ

SHIMIAN ZOU

SUSAN ZULLO

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P R O C E E D I N G S

(8:30 a.m.)

MR. BRUBAKER: Good morning, everyone. Welcome to the workshop. My name is Scott Brubaker. I am the Director of the Division of Human Tissues in the Office of Tissues and Advanced Therapies at CBER FDA. And I'd like to introduce the person who'll give us the opening remarks. It's Dr. Wilson Bryan. And he's the office director and has taken that position or was appointed to that position just last November, in early November. Wilson has been at the FDA at various times for a total of about 13 years. Most recently, he was the Division Director for -- I don't have this memorized yet - the Division of Clinical Evaluation and Pharmacology/Toxicology. So, Wilson, if you could give us some remarks, thanks.

DR. BRYAN: Thank you, Scott and welcome. There are about 200 folks who signed up for this workshop and I think everybody's got a busy schedule. And some of you folks came from a

long way to get here and that represents your interest in this topic and your commitment to the safety of cell and tissue products, so we really do appreciate you being here.

Now, this workshop was put together by the Office of Tissues and Advanced Therapies. This is a new office at the FDA in the Center for Biologics. These products were previously regulated in the Office of Cellular Tissue and Gene Therapies, or OCTGT, but there was a reorganization so, now all these products have moved into OTAT, the Office and Tissues and Advanced Therapies. The Division of Human Tissues, which organized this workshop, was in OCTGT and now has moved into OTAT and is really unchanged with that reorganization.

Now, regulatory requirements include the need to screen and test potential donors of cell and tissue products for Relevant Communicable Disease Agents and Diseases, or what we call RCDADs. But over time, as new infectious diseases emerge, there's a need to designate new additional

RCDADs. While the regulations describe the criteria for identifying new RCDADs, the regulations do not specify the deliberative and scientific processes necessary to apply those criteria.

The goal of this workshop is to generate scientific discussion regarding the types of information available for use when assessing risk. We will discuss ways to better characterize the benefits and risks of cell and tissue transplants during periods of emerging infectious diseases. And we will consider the kinds of data and analyses that are needed to make well-informed decisions. Now, the agenda is full, but there is time for discussion at the end of each session. The success of this workshop is going to depend on your participation in that discussion period, so please be involved.

I want to thank the speakers and moderators who came and have committed to this workshop. There are few from the FDA, but I particularly want to thank our colleagues from the

Centers for Disease Control, from research organizations, from academia, from cell and tissue banking professionals, and particularly the clinicians who use these products to treat their patients. Members of two workshop planning groups -- and these have been on the slides that are rotating through -- two workshop planning groups have been meeting weekly for the past several months to put this workshop together. I want to recognize those two groups and I particularly want to recognize every project like this, every workshop needs a champion, and the champion for this workshop has been Michelle McClure. And, Michelle, I want you to stand up for a second so folks who didn't get the chance to meet you recognize you. And just a round of applause for the folks on the workshop

(Applause) committees. Thank you, Michelle. (Applause) Again, I want to thank you all for being here. We

need you to participate in the

discussions and to inform us. And I look forward to your participation. I'm going to turn it now over to Dr. Michael Strong from Strong Solutions who's going to moderate the first section.

DR. STRONG: Thank you. By the way, Strong Solutions is a phony company. It's just one I had to make up -- in order to come here and get my travel expenses taken care of.

(Laughter) I want to thank the FDA for providing the opportunity to have a tissue bank reunion. I see a lot of people here who have been involved in tissue banking for almost 50 years. You should realize that in the tissue banking field that the U.S. Navy was the first organization that started tissue banking, and there are some of us here who are former members of that organization, and that AATB that you saw up there was started by the Navy. Many of you may not know that.

I was also reminded that when we were doing tissue banking back in the '70s, I think it

was, Bill Tomford right? I think I started in 1970. The infectious disease concern that we had didn't really exist. The only test we were doing was a VDRL, and we all know how valuable that was. But it was the same test that was being done by the blood bankers at the time, and I can remember when the first little Hepatitis B Surface Antigen test came in it was like everybody was blown away that this new technology was coming along. And here we are today and we're going to be talking about a lot of other interesting infectious diseases that have been identified since the early days.

And of course, that was also at the time when stem cell transplants were first started. The cornea people can reach back to, like, 1905 to talk about the first cornea. I think, Ellen, were you there at that -- (Laughter) No, you weren't? (Laughter) Okay, so I know too much and I tried to get out of this, but Scott twisted my arm to come out here just to add a little historical perspective. As mentioned, we'll have a Q and A

at the end of the -- these sessions, and we should start out with Dr. Bollinger talking about emerging infectious diseases in the U.S.

(Silence)

DR. STRONG: So we've got a great start, (Laughter) typical of a meeting of this nature. Somebody forgot to come. So maybe we'll just shift that one in case they show up before the morning is over, so let's skip over to the next one, Mark Roberts.

DR. ROBERTS: Okay, thank you. Thanks for inviting me. I have to admit I feel a little odd because I know virtually nothing about tissues. But what we do at the School of Public Health -- at the Graduate School of Public Health University of Pittsburgh -- is, we've done modeling of the diffusion of infectious diseases and mitigation strategies to prevent them. So I'm going to talk about -- does this not work -- how do I advance it? Sorry, is it not -- oh, it -- mm hmm? It's not advancing when I advance. There it goes. All right; sorry.

So I'm going to talk about our framework for replicating epidemiologic dynamics. I'm going to describe the use in some influenza-like illnesses -- which are the ones that we have the most experience with; things that are transmitted by proximity -- and some predictions we did for BARDA in the 19 -- 2008/2009 (inaudible) examples of how you can use modeling techniques to understand how to predict how much of a disease is present in a particular location.

The Framework for Reconstructing Epidemiologic Dynamics -- or FRED, as we call it -- is a -- it's a large agent-based simulation model that produces works from a basic population, which we call a synthetic population, which represents in our case the entire United States. If you run FRED on the entire population, it's a 315 million agent, agent-based simulation model.

I'll talk a little bit more about the population later, but then each person in this population has behaviors, like they either choose to get vaccinated or not, they choose to go to

work or not, they choose to send their schools -- kids to school or not. There are disease models that represent the natural history of the disease that the person in the simulation may or may not have, and then there's interventions that you can do, such as, you can increase vaccination rates, you can quarantine people, you can do things that intervene and mitigate the effect of that disease.

The way we built this is, we used U.S. census data at the census block level to create individuals who represent at every census block in the United States the exact representation of those diseases, so you -- I mean, of those people, so you have the right gender distribution, household size distribution, age distribution, ethnicity distribution, income distribution for every census block in the United States. They are distributed in those census tracks, or census blocks, by Landsat satellite photography density.

From the Department of Education, we have the location and size of every school in the United States, so since we know the school

districts and we know every household that has school-age children -- every day, children wake up, they go to school, they come back. We also have from the Bureau of Labor Statistics, we have census track by census track how many jobs there are in each one of those census tracks and where they come from. So every day, people get up, they -- some of them go to work, some of them don't, they go back in the -- to their houses at the end of the day.

The model represents -- it uses iterative proportional fitting to fit all this and represents -- this is just from Pittsburgh -- represents pretty much exactly the right distribution of household size, age, race, income, where people go to work, and where people go to school. And then -- I don't know if this is running. This is where I think I -- one of the times I have to switch to my machine, because your -- oh wait, is it -- I can't tell if it's -- this is a simulation that shows the spread of avian influenza across the entire United States. Every

red dot represents a person who has avian influenza that came in, and it -- we had people move; they go according to how many people move from Atlanta to Chicago, how many people go from Chicago to San Francisco and back; and then the green dots that appear, people after they have got -- they've finished with the avian flu, you can keep track of mortality, you can keep track of all kinds of things like that.

The model is then able to predict the impact of interventions, things like what happens if I can treat up to a

percent of the people before they -- in the middle of their symptomatic period? What happens if I increase the vaccination rate, what happens if I make people -- if I close schools, and those kinds of things. And you can see for each one of these interventions, or combinations of those interventions, what that does to the spread of that disease.

During the 2008-2009 H1N1 epidemic, we posted a faculty member down at the Office of the

Assistant Secretary of Public Preparedness and Response, BARDA at HHS and basically what we would do is, that faculty member would be in the morning meetings about, what should we do? You know, there are 14 cases in Texas or something like that; what would happen if we closed schools in Texas and he would call back, we'd run it over the Pittsburgh supercomputer at night -- because when you're running multiple scenarios with 350 million agents, it takes a lot of computational power -- send the results back, and they would discuss them the next day. And we're not convinced that that made a huge amount of difference, but it did make some difference in those decisions. The idea is you can use these models to predict the spread of a disease. You can keep track prevalence of incidence, of mortality, of morbidity, and all those kinds of things in these simulation models.

We also were able to produce for them representative areas of where it made the most sense -- this happens to be in Washington, D.C. -- where it made the most sense to concentrate

vaccination efforts for inhibiting the spread of that disease. And then -- let's see, can you just switch to the web page now? Sorry, that's not -- there you go.

So during the -- we also built, for example, for the measles epidemic that happened out in Disneyland in 2014 -- late 2014. We built a simulator to sort of understand what would happen in different locations of the United States for if -- under different conditions of how many people were vaccinated against measles. So you just saw it to say to

(inaudible) Washington --

(inaudible) was it Virginia? Yeah, we'll do -- well, Alexandria; say it's close to here. So what you will see on the left is a movie of a simulation where if in Alexandria, Virginia only 80 percent of the people that should be vaccinated against measles are vaccinated against measles and we

randomly interject a measles case into that community. And you'll see that there's quite a few people who -- in the blue is the people who are -- have finished their measles outbreak.

And here on the right, you will see the exact same population, the exact same introduction of a measles case if (a)

percent of the people who should be vaccinated are vaccinated. And what you can -- this is a graphical example of the value of herd immunity to stop the progression of a disease. You can keep track of how many cases you would have prevented and things like that. And so we -- and this was a tool that we built so that policymakers and people in different states could look at what their own state, their own county would do under -- how it would fare under different conditions.

Okay, can you move back to the slides? Okay. So, we also did some work postulating --

you know, what happens if you have a new disease that there's no immunity to, there's no vaccine, there's no treatment for something like that, but -- and you don't know very much about it? For example, you don't know its infectivity, you don't know really its R naught; it might be somewhere between two and eight. You don't know how long it's contagious; you don't know exactly how -- what its mortality is. And so we just created -- oh, you know, I think you have to switch back to my computer because I don't think your computer does QuickTime. Sorry. What?

SPEAKER: (inaudible)

DR. ROBERTS: What? Can you switch back to my computer? Sorry. I guess we should start using something other than QuickTime.

In this disease, this is a disease which there's no immunity at all and we look at what would happen under different R naughts and different transmissibility of the disease. And what you see is that the faster the R naught, the more rapidly the disease progresses through the --

through the entire community and the more rapidly it goes away. But because there's no immunity at all and this is a relatively infectious disease, everybody gets infected. Now, what I was planning to do was also show you some examples we have inside FRED. We have vector-based transmission, so if we know the mosquito density of a particular geographic area we can do diseases that transmit by vector.

We also have been introducing and are creating social networks, like sexual networks, needle-sharing networks, so that we can understand the spread of diseases that are not just done by proximity. And for some of the kinds of diseases like Zika and Chikungunya and things like that that you might worry about passing on in a tissue, we are expanding our model to be able to have all kinds of those social networks. So, could you go back to the -- are we at the -- let me see if this works now. No, can you go back to the slides? Sorry.

So when you run those kinds of

simulations, you can find for different kinds of -- every different simulation with a different R naught and a different time of infectivity, you'll get different epidemic curves that you can generate from the data, from the simulation. You can then see what the prevalence is over time, in what kinds of subgroups and where that prevalence mostly is.

And the idea of the -- not only can modeling on this kind of -- at this kind of scale tell you how many people will be infected with a particular disease if it is transmitted in a particular way and if it lasts a certain amount of time, or if -- or how it's -- how virulent it is, it can also tell you on an emerging disease that you don't have much information about -- like, let's say you don't really know its infectivity, you don't know the likelihood of transmission given a particular interaction, be it proximal or sexual interaction or needle-sharing interaction. You can use models like this to understand how important more accurate information about that

particular parameter would be.

You can run sensitivity analyses and say, gosh, if I knew, you know, running what the infectivity like the R naught is across a large range, or the -- how long a person is infectious, or the types of transmission that are available, you can then use the results of the model to demonstrate which parameters you should spend money and resources to go get more accurately to have a better idea of how that disease transmits. And that's all I have to say. So, I think I was within 15 minutes. (Applause)

DR. STRONG: That was QuickTime, all right.

DR. ROBERTS: Yes, right. You guys don't show it.

DR. STRONG: (Laughter) Thank you. Well, I think the Baltimore traffic has thinned out and you've -- Dr. Bollinger has finally made it down south. Are you ready to go?

DR. BOLLINGER: Absolutely, sir.

DR. STRONG: Okay, emerging diseases in

the U.S.

DR. BOLLINGER: I wish I could make that excuse about Baltimore traffic; I was over in Bethesda for meetings the last couple days and left Bethesda on a Uber that took me to the wrong campus drive, so I had to run the last mile to the other campus drive, so I'm very sorry that we're a little bit out of order here. So, I was asked just to introduce the topic of emerging diseases and some general -- in a general way, just to start this off, so I apologize for going out of order.

So, these are just some potential conflict of interest; I don't have any specific conflicts of interest for this talk, but these are just for information's sake. So what I'd like to do, and I'll try to catch up some time as well so we have more time for the other speakers, but the -- what I'd like to do is just generally talk about the definition of what we call emerging diseases, describe a few examples of prior emerging diseases in the United States and

elsewhere and their population impact. And then discuss a couple of examples of emerging diseases and where their potential impact might be.

So, we obviously concern ourselves about emerging diseases for two reasons. One, we're obviously concerned primarily in this audience about the transmission of diseases, emerging diseases, from donor to recipient, but, of course, in clinical infectious diseases most of the things we see are complications related to post-transplant infection, both of which are impacted by emerging infections, emerging diseases.

In general, there's sort of three buckets so -- of emerging diseases so that we can think about -- one would be, diseases that re-emerge in a population where they may have existed before and are now re-introducing themselves. New emerging diseases tend to be zoonotic diseases for the most part and we'll talk about a couple of examples of that. And then I'm just going to say something briefly about

antibiotic resistance as an emerging problem and potentially a problem for transplant donors and recipients.

So one of -- and you heard the previous speaker mention measles. A good example of a re-emerging disease in the United States, of course, was the measles epidemic that occurred in 2014. This is from a New England Journal article in 2014 and since that time we've had about a little shy of 200 cases. So it's come down in 2015 and then further in 2016. So we had this blip in 2014 really, I think, illustrating what you just heard earlier about the importance of having herd immunity and when that doesn't occur in a population these sorts of re-emerging diseases are predictable.

Another one that I'd like to highlight as an example is yellow fever. I'll come back to why I think that's interesting for us to think about in the United States, as well, in a moment, but there was an outbreak of yellow fever in Angola DRC and Northern Uganda. I do some work in

Northern Uganda and I remember when the cases started coming in, people were concerned about all sorts of things, but they didn't initially think about yellow fever. The CDC went in and helped investigate this and realized it was new cases of yellow fever that had not been seen in those areas for decades. And again, it was because immunization had stopped some decades before that and it was re-introduced.

And then you may have seen on the news more recently about outbreaks of yellow fever. I wouldn't necessarily call them urban outbreaks, but they're certainly in new areas on the southeastern coast of Brazil, which has really begun to stress the global supply of yellow fever vaccine, to try to address this. I think they've -- saw recently that the Brazilian government had purchased about 11 or 12 million doses of yellow fever vaccine to try to distribute to this population. I think they've had, I believe, about 80 or 90 -- you know, documented cases in this region and a few deaths, but they don't have

enough vaccine to cover the population at risk, so that's an increasing issue.

I show this picture on the right of the Aedes mosquito, which transmits yellow fever, and that's important to think about because the Aedes mosquito is an issue for us right here in Maryland, because the two species that transmit yellow fever, albopictus and Aedes aegypti, are right here in the United States. The Aedes has been around while; albopictus was introduced through recycled tires in Texas decades ago and then worked its way right up the coast. So if you see those little tiny mosquitoes in the backyard not quite at dusk with stripes on it, black and white stripes, those are your Aedes mosquitoes, and they transmit not only yellow fever but another re-emerging disease.

We had dengue in the United States reported back in the 1800s and it was gone for a long time. And now it's being re-introduced into Key West and other places in the United States. We have the vector, we now have the infection and,

of course, the same mosquitoes transmit West Nile, Chikungunya, and Zika. So we've got the vectors. I suppose the good news is that the albopictus, which has got the most range, is not the most efficient transmitter; Aedes aegypti is a more efficient transmitter of things like yellow fever and dengue, but they're both perfectly capable of initiating epidemics and maintaining epidemics if the outbreaks are large enough. I wouldn't be surprised at all to see some more Zika transmission in Florida and elsewhere in the next season because we certainly have the mosquitoes.

This is a nice -- if you're interested, this is a really great -- I always like to show this paper to my students at Hopkins -- a great paper overviewing emerging diseases from the Journal of Nature in 2008, and this is a heat map from that journal which I really like. I don't think it's changed a whole lot since that time. Oops. I'm not sure we have the -- do we have a pointer? Oh, there we are. Which really distributes the outbreaks of new emerging diseases

by category and these are wildlife zoonosis, which primarily are in Asia and Africa. And, I mean, this would include things like Zika, for instance. And there are domestic zoonosis which are primarily here. Any idea what those likely are? Those are your influenzas. Those are our -- related to chickens and pigs. Those are these -- or the new influenza outbreaks, primarily.

Vector-borne, of course, here, and we've talked about some of those, including those transmitted by Aedes aegypti, but there are others like Nipah virus and others that we need to be worried about -- and drug resistance outbreaks here, although we're now seeing evidence of it in other parts of the world, but initially a lot of it is in places where antibiotic use is less well regulated.

I want to mention another disease; I like parasites, so I thought I'd mention Chagas disease, which I think is an interesting -- and I'm not sure if it's re-emerging. I suspect it's an emerging zoonosis for the north -- southern --

North America. It's very, very common. There are eight to ten million estimated cases of Chagas disease in South America and Central America transmitted by the kissing bug or the reduviid bug, and the interesting thing for us to think about is how prevalent this infection may be in our Latin American population, in our immigrants.

And this map shows one study that highlights all the places where a screening documented evidence of Chagas infection, trypanosomiasis infection around the United States. Although the prevalence is relatively low, it's everywhere. So if you screen enough Latin American donors you're going to find Chagas disease infection. Now, this, of course, has led to recommendations to restrict transplantation of hearts, obviously, because that's -- the heart tends -- the heart is and the bowel are the two targets for this infection.

There's a little bit of uncertainty about whether one can safely transplant other organs from Chagas patients -- donors, but we just

don't have enough information yet. I think at this point it's primarily -- and others in the audience are -- will be more familiar with this -- primarily recommending restricting the heart transplants from these patients. It's a treatable disease so it can be, you know, potentially treated, and donors, for instance, of -- for kidneys and so forth have diagnosed ahead of time.

And so that's really just to emphasize the importance of zoonotic infections which are transmitted primarily by insect vectors, and we have many of those that we've heard about in the news. Ebola being the big one, but we've had outbreaks of Marburg since that time and we'll continue to see cases and outbreaks of Ebola, Marburg, Lassa- related hemorrhagic fevers. MERS, Middle Eastern Respiratory Syndrome, is a big issue in -- primarily in Saudi Arabia and the Gulf, but I know it's of concern for health care workers at Hopkins who end up working over there and doing consultations, getting exposed to MERS. And I've already talked a bit about yellow fever;

you're going to hear more about Zika, so I won't say a whole lot about Zika. Another speaker will address that.

Well, but there are -- the point I want to make is that we really are going to have a difficult time predicting what's the next big SARS or MERS. There are always going to be, you know, Bourbon virus is another one that was recently diagnosed in one patient. We're always going to have new zoonosis that we're going to have to keep our eye out for. And I think whether or not they become issues for transplants really depends on the prevalence, and how quick do they spread, and how we address and stop those epidemics.

So, I'd like to end in a -- with a couple minutes on antibiotic resistance and, you know, we obviously think about antibiotic resistance in transplant patients, post-transplant all the time. It's a huge issue. It's probably the most -- antibiotic resistance and serious infections are our most concerning complication post-transplant for any of those patients. And

we're now seeing, you know, superbugs. There was a patient that just died of -- in Kansas of one of these pan-resistant resistant E. coli. So, whether or not they are issues for donors and things we should be concerned about, there are certainly examples of bacteria being transmitted from donor to recipient, but I wanted to highlight something of -- that's coming and that's to keep in mind my favorite comment from John Bartlett. He reminds us that we are more them than us.

If you are to take the dry weight of a human body and you weigh it, you'll find that the dry weight of the bacterial cells outweigh the human cells, so we are more them than us, and the issue about the microbiome and concerns and discussions and understanding of that is getting increasingly important. And in fact, we're seeing new kinds of transplantations; microbial microbiota transplantation or fecal transplantation, which is becoming a -- in many centers like Hopkins, we're increasingly seeing it being used as a treatment for resistant

(inaudible) infection. There are now animal studies suggesting it might be a treatment for inflammatory bowel diseases, so we may see manipulations of the microbiome as a potential transplant issue moving forward as it gets increasingly important.

I'm going to end with just an illustration. I think -- yeah, I'm often not sure whether this is a good news or bad news story. I'm going to focus on the good news; we need more of that these days. So SARS cost the world $30 billion at least for, you know, less than a hundred cases distributed around the world. It was a huge impact, but I think the good news is illustrated, perhaps -- well, good news/bad news illustrated by this story -- so this is an email that was sent out on February 10, 2003. You won't be able to read it, I don't think, but I'll -- it just says -- it's written by a physician on the ProMED email list for -- many of you are probably

on that list, as I am -- and he sends out this request; he says, anybody heard of an epidemic in Guangdong? An acquaintance of mine from a teacher's chat room reports hospitals there have been closed and people are dying.

So this is February 10, 2003. And it turns out that the epidemic which we now know to be SARS was beginning in that region in November. And there were 300 or 400 cases already by the time that email went out asking about it. And ironically enough, it was the very next day that the alert went out to WHO. The Chinese government finally admitted they had a problem one day after that email went out. And then in a period of eight weeks -- and that's, I think, the good news story -- the world scientists were mobilized, and within eight weeks we went from not knowing we had etiology to publishing the full sequence of the SARS coronavirus on science online, within eight weeks.

So it was an incredible mobilization of epidemiologists, geneticists who rapidly responded

globally to help us understand what was causing this epidemic; identify not only its genomic sequence, but also its source -- its reservoir; and then allowed us to quickly adjust our response. And just imagine, I don't know, if this had taken decades or years -- it took us 20 years to figure out, you know, the cause of HIV/AIDS, probably 15 years from the first cases, really. So, you know, the -- imagine what would have happened if we hadn't had this mobilization and this rapid response -- global rapid response infrastructure in place. So, I think this is a good news story for our ability to identify the next emerging disease quickly, as we did with Ebola. There are other reasons why we could talk about what went wrong with the Ebola response, but certainly diagnosing the cause of that outbreak was very, very rapid.

So, I'm going to finish with just trying to address the question, why are these diseases emerging? This is G.K. Chesterson saying, regarding your article, What's Wrong With the

World, his answer is, I am. And we are; we're the reason why these diseases are emerging. Obviously, poverty; the encroachment of human behavior on animal reservoirs; the just incredible amount of movement of both people and microbes around the world -- this is the flight map just demonstrating how quickly and how much we're connected. And then, finally, zoonosis is exacerbated by exposures that we should avoid, such as the ones that my children are demonstrating here.

(Laughter) Now, I'll give a special prize to anybody that can recognize this fellow right here. I'll give you a hint; Nobel Prize winner of 2008. So this is Luc Montagnier who's about to kiss a tapir and expose himself to zoonosis. So, I happened to snatch that picture from a long time ago, but he was the discoverer of the HIV virus. So we all have our risk behaviors that would increase the likelihood of zoonosis that we need to keep in mind. And I think that's my last slide. Thank

you very much. (Applause)

DR. STRONG: Thanks and thanks for the effort to get over here from beautiful downtown Bethesda. So we'll move right along to estimating disease incidence and prevalence in general and donor populations. Dr. Biggerstaff.

DR. BIGGERSTAFF: Is it all right I move this. Keep

(Laughter) I broke it. There we go. Thank you, whoever did that. Okay, thank you very much. I'll start out with a little background about myself and the outstanding group of people I work with, and discuss general points about incidence and prevalence estimation. My discussion will focus around how we go about this using three basic study types or tools that I have had experience with in our division to tackle this problem, give some illustrations

and list some pros and cons related to those. Finally give a table summary comparing them and end up with some final comments.

I work at the Division of Vector-Borne Diseases, CDC. Many of you are probably familiar with various agents we study there. The most important thing about our division is the variety of expertise we have to be able to do a large variety of work that we do. Various ones are listed there. I like to say we have a lot of "oligists," but I'm an "ician," I'm a statistician in the division. Obviously, a lot of our work is carried out with external collaborators, state and local health departments from many studies, universities and various research organizations.

General points to be made about incidence and prevalence estimation for emerging diseases: obviously, of interest, is defining a population for the inference. This is often driven by the information source in terms of the design being used. A timeframe and geography, I

forgot to list, are very important in these cases. And again, being a statistician, I'm often concerned more than others about the inferential basis for statements made. It's often a mix of statistical and non-statistical or extrapolation-type of justifications.

The information sources often used, or that are used, for these kinds of studies I refer to here as the data. When I refer to the data, I mean the information collected at the time of the study and how that data might be collected ideally from the statistical point of view randomly in some sense or another. Extra information is often used when it comes to these problems; population information, pathogen kinetics and other epidemiological information.

I will give examples of three study types that we have undertaken for these -- for this problem, again, driven largely by different kinds of data sources: community surveys, estimation based on disease surveillance data and I've done now multiple projects using data

collected from blood banking. Community surveys involve populations that are often associated -- the ones I've done have been related to ongoing epidemics or the tail ends of epidemics and so, they're responses and it's of interest to know what happened and what level of concern there should be.

Populations are defined, as I said, geographically and temporally. In this context, those are both typically small; small geographies, short timeframes. It is possible in such settings to estimate incidence or prevalence in subgroups of the population of interest, but that's not often precisely done in this context. Key feature of this approach is that the population is directly sampled and ideally some sort of random sample in terms of statistical inferences done. Although, often some sort of convenience sample is used for logistical reasons or a mix of these two.

In these studies, of course, individuals are sampled and evaluated for evidence of infection using different tools and those are

summarized to provide estimates of incidence and prevalence. The nice thing and important thing about community surveys, it is among three of the only direct measurement of incidence in the population of interest. You might suspect that required resources for this kind of study are huge. It takes a lot of people, a lot of planning, a lot of logistics, laboratory, and epidemiological efforts and also statistical expertise to carry these out rigorously. In addition, local and community health departments are key partners in these kinds of studies.

Here's a list of studies I've been involved with, community surveys, in the U.S. and territories; I've been involved with others internationally. The only one on this list that I wasn't directly involved with was the West Nile survey in Ohio, although I consulted a little bit at the beginning on the design. The pictures there and I was jealous of the last talk -- the last two talks; their graphics were a lot more interesting than mine. These pictures are

sampling designs for teams to go out and sample census blocks or city blocks or such units for different studies. The large one in the southeast corner was from Queens, 1999. The one above it is from the dengue outbreak in Key West. And the other one, I think, was Staten Island. Colors there relate to stratification in the design.

Community surveys have, as all of these do, different pros and cons. Again, the most important aspect, I think, of community surveys is a direct measurement. I say recent and historical infection; that would depend on the type of testing used to determine infection. I assume folks here know about antibody tests and what they can say. These studies also provide a variety of epidemiological information that other studies may not, including information by demographics, age, sex, et cetera. The studies are often used in the epidemiological and outbreak context to get a handle on potential risk factors to try to inform prevention measures, and other epidemiological parameters are estimated from these, as well.

As I mentioned, a challenge to these is, they're very resource-intensive, and they're also -- and very small, geographically. They require a lot of laboratory resources and if you don't have a statistician handy you might have trouble when you come to write it up. And there are potential biases from non-participation; that's probably the biggest one. However, statistical analysis can attempt to address that given population information often available from the census.

The next type of data I have used in this kind of setting has been disease surveillance data, most notably for myself, West Nile virus. The population of interest, I always say that person's bounded geographically and temporally because we always have to keep that in mind, these geographies may be very large or very small -- it depends on what you care about -- and may be short or long-term. Estimation here for subgroups of individuals is much more readily available and the point about these data is, in my examples, that they're collected by public health agencies and so

these data are typically in some sense readily available, at least accessible by public health and sharable that way.

Based on active, passive, or a mix of those enhanced, I guess it's often called, surveillance. One problem with that data source, of course, is it's subject to over and under-reporting and various biases. Here, we -- it provides an indirect measurement of population incidence and prevalence and so statistical and mathematical methods are needed to relate that to the general population. Required resources include, of course, the surveillance data itself, as well as information from epi and -- about epi and biological parameters, and requires a fair bit of statistical expertise and purpose-written software, in my context, to carry out these estimation exercises.

Examples I have been involved with in particular are West Nile virus, Dengue virus, and Chikungunya virus. Using this approach, they've -- typically, these have been done historically.

I've taken essentially disease onset dates for these various diseases and after some time used that and biological and epi information to do the estimation. It is possible, however, to do these in a -- in essentially a real time setting, as some colleagues in Australia did, for example, using my methods in Dengue virus in (inaudible).

The idea is to estimate that -- as always, in a sense, estimate the number of infections in a population, the key observation being that each observed case represents a certain number of infections in the population, scaled by population then, for the risk estimates. Biological and epi parameters required to do this include asymptomatic proportion incubation period and virus duration in tissues and blood -- which is tissue, I guess; remember, I'm a statistician. Surveillance coverage in this context is absolutely key. For all of our West Nile studies in the United States, we assumed essentially complete ascertainment of such cases because we use individuals with West Nile virus neuroinvasive

disease and we felt that that was -- any insufficiencies there were going to be negligible in the context at hand.

In a project in Puerto Rico for Dengue virus, however, Dengue virus surveillance is known to be quite under-covered and so, in particular, in our context we used information and arrived at an estimate of about 15 infections per reported case were needed to reflect under-coverage of (inaudible) and that's critical. Obviously, population size data are available, permitting estimation by subgroups.

This is just a slide to illustrate the kind of results available and information that goes into this kind of estimation problem. I won't go through the table. The top graph illustrates the -- what I call the data; that's an epidemic curve for West Nile virus cases in Colorado in 2003, so the height of each pin represents the number of cases reporting onset on that date that year. The result then, the

take-home message is the panel on the bottom which is an estimated risk curve and, in fact, this was for transfusion risk, so yeah. And then the summaries for that curve are available on the right. So that's the take-home message from this kind of exercise.

Recently, I have applied -- I have augmented those methods used for transfusion and applied them to -- for tissue risk estimation, for the geographies given there and the different tissues listed there. I was able to do this by age group, as well. I mentioned I -- subgroups were possible in this context. This was work supported by the AATB and results so far are unpublished, but I will be getting to that.

The last -- how am I doing? Well, I'm not awful. The last data type -- oh, I'm sorry. This is the pros and cons. What's good: well, the data in some sense are available if you work at the CDC, I suppose, or with any other public health agency or you know people who will get it to you. In some sense, it's routinely collected

by public health agencies at various governmental levels. A nice thing about this is the scales can be large if you need them to be, but they needn't be. Subgroups estimation is very -- is available as well. These methods do, however, depend a lot on external information in some sense, epidemiological and biological parameter estimates. As I mentioned, subgroup surveillance coverage is key and so you may need to set about understanding the surveillance system and its shortcomings to do this well. Potential biases are greater; surveillance biases and information for the parameters needed. Again, these are typically retrospective and so can give a sense of how bad it might be, but not necessarily how bad it's going to be. And these can -- these approaches are fairly statistically involved and so you hug a statistician.

The last type of data I have used are data collected by blood banking organizations and then these are collaborations with them. Again, population of interest geographically and

temporally; these may also be large geographically or small and may be short or large timeframes. There is an extrapolation here to non-donors and in particular, children and so this is a shortcoming here in this context. The data are collected; they do require a fair bit of testing of banked data specific for the project at hand and so that requires (inaudible) of resources and so collaboration with such organizations is key from our perspective at CDC.

A benefit of this approach is, these results can be done essentially in real time, as data are -- or as donations are collected and then tested in these -- this day and age often very rapidly. It is a -- can provide a direct measurement of current infections and I put, however, that detection, depending on the assays used -- and I didn't -- I wasn't careful enough with this slide -- detection may be transient, depending of the type of assay. If it's a nucleic acid test, that detection will be transient, I believe, but if you based it on antibodies and use

long term antibodies then, not so much. Again, statistical and mathematical methods are used to relate these estimates to population infection estimates requiring, as before, epidemiological and biological parameters for risk estimation, population size. And again, keep a statistician in your pocket.

Examples I've been involved with here include West Nile virus for both North Dakota and Texas, in particular. I know colleagues in the blood banking industry have also carried out their own exercises, as well. Chikungunya virus and Zika virus, that paper is currently under revision and hopefully, will be accepted soon. Again, the idea behind -- oh, I'm over; I apologize. The idea behind blood collection data is to estimate the number of infections in the population and requires the input parameters used for the surveillance approach as well.

These are the kinds of results available from the -- this approach; these were incident infections in the Dallas- Fort Worth West Nile

virus outbreak in 2012 and historical cumulative infection estimates from North Dakota, also West Nile virus. Pros and cons: you have to be able to test all of these things and, as I said, the geographic and temporal scales can be whatever you care about. The potential problems with this approach are largely biases related to blood donors versus the general population. And of course, it required testing of all these bank samples.

Here's a table I won't detail, really. The key points were: community surveys, you can estimate incidence and prevalence directly in the population at the time -- about the time of interest. Surveillance data, a key aspect there is, it can be time-dependent, and geographic and temporal scales can be large. And blood collection, the real benefit, I think, of blood collection approach is that it is real time. In the interest of time, you can read my concluding remarks; I said those things several times. Thank you. (Applause) Okay. (Laughter)

DR. STRONG: Not to worry; we're doing great. Right on the money. Okay, our last speaker for this morning's session. All right, you ready to go there?

DR. BRAMBILLA: Yeah.

DR. STRONG: Dr. Brambilla will be talking about the same topic, except we're focusing on HTP -- HCT/P donor populations. Thank you.

DR. BRAMBILLA: Just a brief historical note before we get started. In the 1790s the federal government was located in Philadelphia before -- well, when things got started. They exited Philadelphia, more or less, in a panic because of an outbreak of yellow fever that was brought by sailing ships coming up from the Caribbean and this was apparently a seasonal occurrence in that time and even showed up in Amsterdam. So, we've been dealing with these kinds of problems for a while.

Anyway, so I'm going to talk about estimating disease incidence and prevalence in the

HCT/P donor population. How do I advance the slides? Is that on the keyboard or is that on -- wow, convenient. Basically, what I'm going to present draws on my experience in two studies, the first one is the Recipient Epidemiology and Donor Evaluation Study- III, REDS-III.

The REDS program, originally called the Retrovirus Epidemiology Donor Study, has been in existence since the late '80s, funded by NHLBI. The original target, of course, was HIV and the blood supply. The project started seven years before NAT testing was available. It has evolved and our targets have evolved. We're still interested in the safety of blood supply and availability of blood transfusion. I'm also going to talk about some -- draw on the experience in the Tissue and Organ Donor Epidemiology Study, which I will refer to henceforth as TODES because that's what we call it. So, let's proceed.

I want to start by talking about what we do in blood donors, because that's both estimating incidence and prevalence in blood donors. First,

talk a little bit about the data requirements for this and second, the methods of estimation. And then we'll talk about available data from the HCT/P donors, the results -- what the results of TODES show us. So what we know about methods from blood donors and can it be applied to tissue and organ donors at this point?

We need reliable determinations of which donors -- I should say, donors are infected and which are not. So we need tests that are both highly sensitive and highly specific. Sensitivity, of course, being the probability that you actually get a positive test from an infected person, and specificity is probability that you get a negative test from an uninfected person. The problem is that if you perform a given assay there is a trade-off between sensitivity and specificity, depending on where you set the cutoff -- most of you probably already know this -- where you set the cutoff on the assay for what's a -- an optical density that's high enough to say we have a signal. You're either going to increase

sensitivity and decrease specificity or do the reverse, depending -- as you raise and lower the cutoff.

And it's just -- the curve on the left illustrates this. I showed two possible cutoffs. How do you turn -- oh, there we go. Two possible cutoffs and the upper cutoff has lower sensitivity and higher specificity. So, that's our issue when we do a single type of test. What we want to do in blood banking is find as many infected donors as possible and so the first stage in testing is to use screening assays which are highly sensitive and have lower specificity, so we have an appreciable false positive rate. We then do confirmatory testing of positive screens to rule out the false positives, so using a different testing approach from the original. So, we require data from the confirmatory test for estimating incidence and prevalence; that's how we get to our reliable data.

Just to illustrate the problem on the -- here is a hypothetical example of a million donors

with an infection prevalence of 1 in 10,000 and a test sensitivity of 99.9 percent, so one in a thousand false positives -- false negatives. And then in -- on the left you see I set the specificity at the same level. I'm not getting that -- there we are. And here's the problem: the test result, you still -- out of 999,900 uninfected individuals with this specificity you're going to get a thousand false positives and ninety-nine to a hundred true positives, so you're going to have a very high false positive rate. Now, over here, if I set the specificity ten-fold higher than the sensitivity, then I'm down to one to one; I still have a high false positive rate, and that just illustrates the problem to the kind of thing we're getting into and why we do the confirmatory test.

Now, there -- for -- a little bit about prevalence. There are literature on -- in -- particularly, in journals like Transfusion and Vox Sanguinis, there are numerous estimates of the prevalence of HIV, hepatitis C, hepatitis B, and

so on in blood donors. Some investigators focus only on first-time donors, reasoning that a -- an infection in a repeat donor because it's a new infection is an incident infection, not a prevalent infection; that seems to be -- that's the argument that's made. Some use -- present both first-time donors and repeat donors but do it separately and some use all -- present data for all donors combined. And occasionally, those who present separate estimates for first- time repeat donors separately also present the combined estimates.

When you look at first-time donors' cases, prevalence is just cases over donors. For repeat donors and all donors, it's calculated as cases over donations, so you're getting multiple donations from the same individual, but typically the donation series ends with an infection if that person is infected, so it's always the last donation that's infected -- unless somebody comes back in afterwards and tries to donate again. What should we do with HCT/P donors if we have

multiple donations, that is, multiple organs or tissues from the same donor? Do we do this at the donor level, or do we do this at the donation level? Something to decide.

But the main thing for blood donors is that in blood banking there is much stronger incidence -- interest in incidence than in prevalence, and the reason is because incidence is used to estimate residual risk, which is simply the incidence rate multiplied by the duration of the window period, which is the period of time after initial infection and before the infection can be detected. That's the probability that an infection sneaks through the testing system. So, an infection that's detected is a transmission that's prevented. One that sneaks through is a transmission that can occur. So, that's -- the focus of my blood banking colleagues is on residual risk and hence, on incidence rather than prevalence.

Now, let's talk about how incidence is calculated in this group and I'll start with

repeat donors because this is where most of the work has been done. Basically, it's a classical sort of application of incidence, the way you would estimate incidence in a longitudinal study. First-time donors provide cross-sectional data and we can estimate incidence using recently developed assays that allow us to identify recent infections and separate them from longer-standing infections, for example, an infection that happened in the last hundred-and-twenty days separate from an infection that happened more than a-hundred-and-twenty days ago. In both cases, we're estimating incidence as cases over person time, or person times as a total follow-up time of all the donors included in the estimate. So, let's talk about the methods a little bit.

So, for repeat donors, the first thing we do is to find an estimation interval and typically two years is used rather than one year just to increase the -- or to reduce the standard error of the estimate, get a little bit larger sample size. Select donors with at least two

donations in the estimation interval, excluding any donations that happened after the first one at which infection is detected and if the donor's negative at all donations then that person contributes time from the first donation to the last donation in the interval to the denominator of the incidence calculation. If infected, the convention is to go from the first donation in the estimation interval to halfway between the last uninfected donation and the infected donation, is the time measure. Cases are just those or new infections that are identified in the interval.

So, just to illustrate this graphically for -- very quickly, the solid line is the person time that's included in the estimate; the dotted line, person time that's excluded; this is an infected donation; the open symbol is an uninfected donation; and the arrow gives us the assumed time to infection. So, what you have here on the first donor number one is just the estimation interval goes from here to here, so time from the first donation to midway between the

last two, because this person's infected at the last donation. Same here, but there's only two, so it's just half of the single interval; no contributions from this donor because there's only one donation in the interval; uninfected donor throughout, so from first to last, and no contribution from this donor because there's only one in the interval. That just illustrates how these things are put together.

Mind you, there are, in the literature, at least six other methods for calculating incidence in repeat blood donors. We ran a simulation study to look at these. It should be out shortly in Transfusion; it hasn't been published as of the latest issue. They all differ in terms of how cases are selected and how person time is accumulated. The other six methods are -- three of the methods are biased under all the test conditions that we looked at and three of the methods are biased under most of the test conditions that we looked at. The only reliable method which goes back to George Schreiber's paper

from 1996 is the one I just showed you. The others should be avoided. They are often developed because people want to do things like get less detailed data than what we require for this kind of estimation method, but they cause trouble.

Now, first-time donors -- cross-sectional data only, one donation per donor, so we're going to use the assays and separate recent infections from longer-standing infections. These are either going to be nucleic acid tests where you say that this person has virus detected on a nucleic acid test, but doesn't yet have antibodies, so they're in that narrow window early on; or serological assays that can separate, say, infections in the last four -- a hundred twenty days -- depends on the virus and the test -- from longer-standing infections. And then we use the recent infections and the uninfected donors to calculate incidence in this group. And again, you're looking at this from the point of view of a longitudinal study even though you've got

cross-sectional data. I'll show that.

So let's assume you've got a hundred-and-twenty-day period for a recent infection. An infection is labeled recent happened in the last hundred-and-twenty days. So, we're classifying our first-time donors as uninfected, recently infected, or infected, but not recently -- longer-standing infections. We're going to treat this as if it's a one-hundred-and-twenty-day longitudinal study. So, the donors who are infected more than a-hundred-and-twenty days ago were infected at the start of that hundred-and-twenty-day interval; those are the prevalent cases that would be excluded from a longitudinal study of incidence. The uninfected donors contribute the entire hundred-and-twenty days to time at risk, and the infected donors contribute half of that. Again, we're putting the infection at the halfway point. It's really that simple, so this is really equivalent -- as I said, equivalent to a hundred-and-twenty-day longitudinal study.

All right, I just said all this, so let's go on. Now, basically, just a summary. The first we require is reliable data. We have to have confirmed results because with the screening tests to identify as many infections as we can, we have a high false positive rate and that means that our estimates of prevalence and incidence aren't going to be reliable unless we have -- do further testing to eliminate the false positives. Second, we need -- for the methods that we typically use with blood donors, we need longitudinal data or cross-sectional data that can be treated longitudinally; one or the other.

Now, the Tissue and Organ Donor Epidemiology Study, this is an exploratory study that had three goals. How am I doing on time? Oh, okay. They develop the framework for collecting and analyzing demographic screening and infectious disease testing data in a standardized manner from deceased organ tissue and eye donors; identify challenges to data collection -- to collecting data in a consistent standardized

format; and identify limitations and sources of bias from data captured in this study. So what we're trying to do is say, what's the current state of data collection in this framework, tissue and organ donation? And what are the barriers to getting to reliable estimates of incidence and prevalence?

Data sources for this study were the United Network of Organ Sharing, UNOS; nine organ procurement organizations, which is a rather small subset of a total, including organ donations and -- they provide organ donations and tissue donation -- data on organ donations and tissue donations for eye banks. We excluded tissue processing banks because tissues from a donor may go to multiple facilities. And we had no way of tracking the same donor to different facilities because at each facility a different donor ID was assigned to the tissue coming in.

So, we -- the first barrier we ran into was that some centers weren't willing to participate. The lack of interest in this study;

lack of resources to participate; training on software at the time of the study from one inventory system to another; or, recent participation in another similar study which limited interest in going on. The second problem we found was that data-collected by OPOs and tissue banks are collected for business purposes and/or to support donor- recipient matching. It's not designed for research and surveillance. There isn't a surveillance system in place. That's -- more things we identified is inconsistent use of pre-donation screening tools. In blood banking, people have questionnaires about risky behaviors. You know, have -- if you're a man, have you had -- recently had sex with a man, or do you use needles, drugs, and so on. These questions are asked and screen out some people, but this is inconsistently used in the tissue and organ donation field.

Variation in the order of testing -- whether the screening tools were applied before or after the actual testing of the donor; mixing of

test modality; serology versus NAT. We're moving more towards NAT; more and more NAT in this field, so this is becoming less of a problem. But the tests differ; there's no standardization of which NAT test is used, so differences in sensitivity and the like. And then a mixture of screening and diagnostic tests with differing sensitivity and specificity, so you don't tend to see the screening test followed by the confirmatory test that we see in blood banking. Yeah, inconsistent use of confirmatory tests for positive or indeterminate results.

Missing test results; we had a problem with that, as well. No longitudinal data for incidence calculations and no data to identify recent infections that would allow us to do what we do with the first-time donors. Variation in reporting; some positive results that are in the OPO databases were not found in UNOS and vice versa. Lack of an assigned donor ID that would allow linkage of donations across facilities; a given donor may provide organs and tissues that go

to different facilities, but they're not trackable back to the -- back to a single donor.

So the questions that we have to address if we're going to go to looking at incidence and prevalence in tissue and organ donation is, can we improve the reliability of the data, sensitivity and specificity? Can we improve the consistency of methods across sites? I think that's key to improving reliability of the data and consistency of reporting -- same thing. Can we obtain longitudinal data if we want to do incidence calculations? If we can't do that, can we implement methods for incidence estimation that uses cross- sectional data?

I keep harping on incidence calculations because, as I said, the interest in blood banking is in residual risk; the infections that are not detected, not the infections that are detected. And I think eventually we need to get to the same thing here. Can we estimate risk, especially residual risk, without longitudinal data, as we do for first-time donors? I think that's it. That's

it. All right. (Applause)

DR. STRONG: Could we ask the speakers to join us at the table here? All right, we have a little bit of time for questions for our speakers. Are there any, you know, we have a set of questions that we're going to address relative to this topic, but I wondered if there's anybody in the audience who was interested in -- or had questions to ask any of the speakers. Do you have any questions for each other?

DR. BRAMBILLA: Well, so, a lot of the examples -- all the examples -- and modeling and all that we've -- we saw seemed to be based on infections that -- acute infections followed by clearance rather than chronic infections like HIV and hepatitis C. How does that change things in terms of what you're modeling, in particular?

DR. ROBERTS: So, we actually are advancing the modeling capabilities we're having and, in fact, both HIV and hepatitis C we're putting into the model. You have to make them, the populations, much more dynamic; they have to

age, they have to get other diseases, they have to move around, they have to get married and divorced and all, if you -- if you're going to be looking over a -- the span of hepatitis C, which is a lifetime pretty much, and HIV, which is 20 or 30 years now, and so we're make -- we are in the process of doing that. We have a grant from the Robert Wood Johnson Foundation to expand to a more dynamic population. And we are specifically currently working on including HIV and hepatitis C to represent diseases that stay there once you get them. We just -- we have -- our group is not there yet. There are other groups that have done that already, so...

DR. STRONG: The first question that's posed to the panel is, are there examples where estimates for an emerging infectious disease were done well or were off the mark, and what factors contributed to that outcome?

DR. BIGGERSTAFF: Can we hear me? Regarding some estimates, there were evaluations of two outbreak situations that I was involved

with. One was West Nile virus estimation, in particular, in the Detroit Metropolitan area; I forget the year and then also, Dengue virus. I also forget the year for that; that was in Puerto Rico.

In the Detroit setting, what occurred was -- and this was risk for transfusion, so blood collections. I had used my approach with the surveillance data, came up with a time-dependent curve that I showed an example of, and was told when -- what stretch of time the donations were collected for testing. So I produced estimates and based on that I gave an estimate of how many positives I thought they should expect to see with a range I get to give. I get to fudge, being a statistician; I like to be right 95 percent of the time.

(Laughter) That's funny then -- so I gave an estimate of what they should find, based on my approach. They tested all of those samples and it was a good day because I got

it right, actually. I told them four; they found four. The key answer there is, averages are amazing. That's what it boils down to.

Similar outcome with the dengue study in Puerto Rico. It was -- I might have been off one in that one. But again, it boils down to averages. If you have decent input information, averages you get to where you need to be. I'm not aware of studies that I didn't get right, so (Laughter) I would report those if I knew about them. (Laughter) Those are the only two instances mine have had any kind of verification. Something ideal would be, for example, to take blood bank estimates and do a community survey and see how those lined up. That would cost a whole lot of money. Yeah.

DR. STRONG: Well, I have a question

about reliability of surveys, because in the blood donor situation the estimates -- as you mentioned, there have been a number of studies and the estimates suggest that we should be seeing a risk of maybe one in a million for HIV, something in that neighborhood. If those estimates are accurate, it would suggest that we should be seeing somewhere between 20 and 30 cases of HIV, HCV, HBV from donor transmissions each year. And as far as I know those have not been reported, so is it because the estimates are wrong or is it because we don't have a good reporting system?

DR. BIGGERSTAFF: Is that for me?

(Laughter)

DR. STRONG: It's for anybody.

DR. BIGGERSTAFF: Okay. I'm not going to field that because I don't know anything about HIV (Laughter) or the estimates or how they were done for that, so. (Laughter)

DR. BRAMBILLA: Well, they -- so, assuming we have a reliable estimate of the window period during which HIV is not detectable, and the

second assumption that underlies that is that when you say, when you multiply the length of that window period times the incidence rate, you're assuming that you are -- you can infect another individual if you donate on any day in that window period; that they're all equivalent days. And that's a -- because what you're doing is you're treating that window as a random sample of the entire -- of the -- of, let's say, a one-year period, which is -- because it's like you're taking it, incidence, and reducing it to infections per one person a year. And that -- there's -- so there's some hidden assumptions there that may not be true.

It's possible that people change their behavior, too. You know, I went out and did something foolish, and so I'm not going to go donate blood today. You know, I -- we don't know about that. But there are a number of assumptions that underlie that estimation that may be off a bit.

DR. BOLLINGER: I had a question about

the way the testing is done. If you're relying only on a single screening test to determine whether the -- it's a positive test, then in a low prevalence population like blood donors these days you're going to have more false positives than real positives, so if it's a confirmed test, as you would do to diagnose a patient, you wouldn't just rely on a single test; you'd repeat the test with another one. But if your blood screening estimates are based on a single test, then it's probably false positives were the issue.

DR. STRONG: Don, you want to comment on that?

DR. BRAMBILLA: Well, I -- yeah, we were looking at the data in Brazil from registries working in Brazil as well as in the U.S. and there's a -- the confirmatory tests rule out a fair number of -- a fairly large fraction on the initial positives, exactly which you'd expect; that's what you're saying.

DR. STRONG: I think the question I was raising is really with the confirmed positives and

the estimates that -- of the incidence of infections based on confirmed positives, which is what most of the data's been based on.

DR. BOLLINGER: Well, if any of those -- if they're antibody tests -- both are antibody tests; that would be one issue. If they're viral load tests, that's a whole different issue. I mean, they could be antibody positive, would have such low viral load because they're either on treatment or for whatever other reason they wouldn't be likely to transmit. But I don't have much experience with that, perhaps, Don.

DR. STRONG: Well, in the case of blood donors, it would be both in many instances because there's both nucleic acid testing and serological testing going on.

DR. BOLLINGER: So if you're basing it on viral load testing, then those are infectious, and so I'd -- I guess I don't have an answer to your question in that setting. If they're based on antibody tests, I think they're different.

DR. STRONG: Yes, Melissa?

DR. GREENWALD: Oh. So, Dr. Brambilla --

DR. BRAMBILLA: Yeah.

DR. GREENWALD: -- I was hoping to see if you would expand a little bit when you talked about in the Tissue and Organ Donor Epi Study, the inconsistent use of the donor history questionnaires. I can think of multiple ways to sort of interpret that. And I'm wondering if it has more to do with using questionnaires that are different from one place to another or if you're talking about, like, an organ donor's testing may be performed before or after different time points with -- in comparison to when the questionnaire is administered to family members, the fact that you're asking family members, you have --

DR. BRAMBILLA: Yeah.

DR. GREENWALD: -- to, instead of the donors only. Could you expand upon what it is that you found in the study?

DR. BRAMBILLA: I think there are a couple things. First of all, there's no

standardization of the questionnaire; that's the first problem. There's no standardization of the questionnaire, and so they vary from, you know, center to center. Whether they are actually -- whether the questionnaires are actually used or not, I think, varies from center to center, as well. As you said, you're asking family members; you're not asking -- you don't see blood donors and tissue and organ donors is, if the tissue and organ donor's deceased, you're not going to ask that person the questions that you would ask of a blood donor when they come in to donate blood. So, how reliable is the information is the other problem.

DR. STRONG: Okay, Matt.

DR. KUEHNERT: I was just going to try to shed some light on the question before, concerning why don't we see so many HIV transfusion transmissions and actually I'm going to try to address that in part of my talk. But what you might want to think about is just in terms of --

SPEAKER: Do you mind identifying yourself, sir?

DR. KUEHNERT: Oh, I'm sorry. Matt Kuehnert from the CDC. And so, you know, the things to think about is, one, that the blood transfusion recipients are still. They often die before they might come to be recognized as having HIV infection. And there's a bunch of layers that have to happen, go through before it comes to light. So, it could be that the modeling overestimates the number of transmissions, or it could be that they happen and we just don't notice them.

DR. STRONG: Okay and were there other comments on that? All right, moving onto the second question, what do you see as the major limitations in making estimates for the general population and for the potential HCT/P donor population?

DR. BRAMBILLA: Well, if you talk about going from blood donors to the general population, Brad was talking about this a little bit, but

blood donors are not necessarily representative of the general population. In the blood banking community, we -- we're focused on the blood donors themselves, because they -- because the concern is with risk to transfusion recipients, not to a population level estimation. And, yeah, you pointed out that people under 16 years of age -- actually, I think that varies by state --

DR. BIGGERSTAFF: Yeah, maybe.

DR. BRAMBILLA: -- as to what the actual limit is -- don't donate blood. Blood donors are volunteers and that is a self-selected group, and probably different in behavior from large segments of the population, as well, so I think it's very difficult to extrapolate from blood donors to the general population.

DR. BIGGERSTAFF: One thing I've done in that context, at least among individuals of blood donor age, is to try to use demographic information for donors, say, simple information like age group and sex and essentially calibrate that to the population distribution that we're

inferring to, to try to essentially tune the prevalence estimates or incidence estimates from the donors to the population --

SPEAKER: Right.

DR. BIGGERSTAFF: -- age and sex distributions.

DR. ROBERTS: We've done some (inaudible) related to understanding (inaudible) sorry. We've done some work for the state of Pennsylvania, who wanted to know for their Medicaid program how many cases of hepatitis C they might have to treat if people started getting screening and treated now that there's all the advertising for treating of hepatitis C, because they believe they only know about 50 percent of the cases.

So one of the things that you can do and you could do this in the blood donor versus tissue donor community as well, is, you do have data that

produce -- like, so we know how many Medicaid patients had liver transplants, prostatic carcinoma, other things like that, and since we have a biologic model of hepatitis C that can -- that produces those outcomes, we can tune that model to produce the outcomes you actually saw and back-infer how much prevalence there has to be in order to produce those observed outcomes that you found. And you could do the same thing in the -- if you knew something about the differences in between blood donors and how they responded and how -- what locations they were in and things like that. So I think you can use reasonably sophisticated biologic modeling to back-predict the population prevalence of things, given observed data that you know from special populations.

DR. BRAMBILLA: Yeah. Going back to something that Brad said about Puerto Rico, which was -- what was it? Fifteen times was the estimate you used for dengue?

DR. BIGGERSTAFF: Yeah, that's right.

DR. BRAMBILLA: Yeah, okay. We looked at --

DR. BIGGERSTAFF: (Inaudible)

DR. BRAMBILLA: Yeah, we looked at dengue in blood donors in Brazil, in Rio in particular, during an epidemic in 2012. The epidemic's happening during the rainy season, January to May. And we looked at about -- oh God, I think it was 60,000 blood donors or something like that and calculated the prevalence of dengue in the blood donors over that time period. And then took the total number of cases reported to public health and divided by the population size of Rio and got two hugely different numbers. We had much higher prevalence in the blood donors because we're picking up -- people come in to donate blood. They're not running the raging fevers and the headaches and all that of dengue. These are people who are asymptomatic, but they're infected, and that's a large share of the donors in Rio, as well. That's a big problem we're trying to extrapolate.

DR. STRONG: In terms of the donor population, since we're on that topic, we have a tendency -- in this setting, at least, we're lumping stem cell donors, bone marrow donors and tissue donors. And it seems to me that those might be quite different populations since the bone marrow/stem cell donors are screened, are interviewed, and give medical histories, whereas, the tissue donors are based on a second party interview. So do you think that those populations should be treated differently in terms of estimates of risk?

DR. BRAMBILLA: I don't -- I guess I think that the questionnaires that are given to probably family members mostly of the deceased are probably less reliable than the questionnaires that are applied to the donors themselves. We already know that the questionnaire responses that blood donors provide are semi-reliable. There's a fairly large number of gay men who don't admit to being gay and go ahead and donate blood. This is one example. I don't know about other examples

like drug use and the like, but some we turned up in REDS, so I think it's -- to me, this sort of a tool to rule out the people who are willing to admit to something, but beyond that, like travel bans, have you been to a country where there's an infectious disease emerging and that kind of thing, but beyond that I think I would not count on questionnaire data for anything other than ruling out the people who say "yes" because they're not reliable, other than that.

DR. ROBERTS: I would agree with that. One of the problems we've had with putting social networks into our large simulation models, is when we're trying to represent the sexual networks that occur between both men and women, and men and men who have sex with men, that if you look at the survey data, there have been lots and lots of longitudinal and cross- sectional surveys of how many sexual partners do you have over time, and how many have you had for your entire life, and how many do you have now, and things like that, and what's interesting is in virtually all of

those surveys, the survey data itself is internally inconsistent. So, if you look at, for example, by age, how many men, say, by a certain age, how many partners they say they had, and how many times a year they have partners, and you ask the same thing of women. Well, in fact, the numbers ought to add up, that if I had sex with a woman, and the woman had sex with that man and you get wildly different answers about how many times that took place. So, even in the context of reasonably well done surveys, the survey data is internally inconsistent. So, I'm not sure that you can rely -- especially when many of the diseases that one worries about are transmitted by things that people are not always so willing to describe.

DR. STRONG: Well, this sort of leads us to the next question, which is, what types of available information can be extrapolated to make estimates for these donor populations? And I think, again, we're asked about HCTPs, but I really think those two populations -- stem cell

donors versus deceased donors -- are different. How would you model those two populations to get an estimate of risk?

DR. ROBERTS: I think that's really hard. In order to do it, what you're trying to do is model things that you don't directly measure and so what I think you would need to do is you would need to find the things in those populations that you can measure. And then some understanding of the relationship between what you're measuring in the real world and what has to have been true in order for that real measurement to appear and then you can represent in a model what you would have had to have had gone on to produce what you actually did see and then back infer. That worked for some things, I don't think it works for all things, especially if the risk is not directly related to something that you can measure -- some outcome or some characteristic you can measure. So, I actually think it's hard.

DR. STRONG: I think we would all agree. It's hard. Jay? We have a microphone there.

DR. FISHMAN: Thank you.

DR. STRONG: Identify yourself (inaudible).

DR. FISHMAN: One of the cleanest models we can get is for the stem cell population, because the -- Jay Fishman, from Mass General Hospital -- because the immunosuppressed host is a much better readout for what you've actually transmitted after the fact, unfortunately. So, I think they probably should be analyzed separately, in that regard, both because reporting can be more rigorous and because they are less likely to have asymptomatic infection, but then you have to back fix your models. Those data are not used routinely, both for solid organ nor for stem cell transplants, are not used to adjust and I expect Matt Kuehnert will touch on this later, but, or not, tee hee, but the reality is, is that, that's the cleanest model we have because you want to know what the risk is to the general population. Look at the most susceptible population, and we don't do that, and we don't capture those data

adequately by design. And so that would be a place where we could improve the models. We would predict that you would have five cases of X, in fact you have 50, there's something wrong with model.

DR. STRONG: So would you propose a study, we're brainstorming here, a study in which you would then do exactly what you're saying in that recipient population, because actually many of the emerging infectious diseases that we've identified have come from the immune-suppressed population, so a study wouldn't be to do what you're suggesting. The issue for me would be, how would you also do that in say tissue recipients, with all the different kinds of tissues that are transplanted, that are not immunosuppressed?

DR. FISHMAN: It's also not the same donor population, of course, but it's much harder. I think if you had in each group, mandatory but blame-free reporting, you could assemble some data around specific pathogens -- in the incidence of those specific pathogens, so if you culture stem

cells, for example, you get a certain number of bacterial or fungal contaminations, how many of those actually result in transmissions? Very, very few, so the reality is, what you want is a readout in a susceptible population. And if you have blood tests, great, in that population, but that is the population where disease is more likely to amplify than in other groups and therefore, you're more likely to see it downstream.

DR. STRONG: Identify yourself.

DR. MACSAI: Marian Macsai -- North Shore University Health System, University of Chicago. I think there's one problem. We haven't tested the recipients at all, so --

DR. FISHMAN: We tested (inaudible)

DR. MACSAI: Pre-transfusion.

DR. FISHMAN: Pre-anything, yes (inaudible).

DR. MACSAI: Pre-transplant?

DR. FISHMAN: Oh, yeah. We evaluate them to make sure they're not going to react

(inaudible).

DR. MACSAI: Pre-tissue transplant?

DR. FISHMAN: (inaudible)

DR. MACSAI: That's what I was talking about.

DR. FISHMAN: Stem cell recipients.

DR. MACSAI: Right. Right. Because pre-tissue transplant we're not testing. Pre-tissue transplant, we are not testing the recipients and that makes for a big unknown.

DR. FISHMAN: Yeah.

DR. STRONG: So, perhaps we've come to at least one agreement, is that there are two different populations involved in this HCTP group.

DR. McFARLAND: Right and Richard McFarland, OTAT. Since I have the microphone I'm going to ask a question and interject. One of the other heterogeneous donor populations we haven't mentioned -- the most frequent repeat donors, which are semen donors, which is a whole different epidemiology than either the cadaveric donors or the stem cell donors and I think when you take

those into account. So, we've got heterogeneous donors and testing. I'm the associate director for policy in the office and one thing that concerns me is we have all these heterogeneities and unknowns in the tissue situation, many more arguably unknowns than we do in the blood donor situation. But when there is an emerging infectious disease, or a recurring infectious disease, we need to make policy decisions real-time. So, Dr. Roberts, mentioning it being downtown when the swine flu was going on is something, but with all these heterogeneities, it makes it difficult to make a policy decision with really loose data. So, my question is how quickly can figuratively we expect in the next model, knowing that it's difficult to predict what's the next emerging infectious disease, of ways to reduce the time lag between it becoming recognized, and having some sort of recognizable model for us to make a policy decision on?

DR. ROBERTS: Well, let me say that I think you're right. You can't model things

without any data at all. I do that all the time, but they're useless, right, so (laughter) - -

SPEAKER: I could make policy

(inaudible)

DR. ROBERTS: Right, right, right. Making predictions is hard, especially about the future. But the fact of the matter is, we know a reasonable amount about the biology of some of these things and we know some things about the kinds of vectors and the kinds of transmissions that occur, so one of the things that we have argued, and I think it's been true in many cases, is that models can be used to direct what pieces of information you need to know the most, to narrow your estimates of where things are and where they will go next the most. And so you have lots of uncertainties about the parameters, about the spread of an emerging new disease. You have lots of uncertainties about its virulence; and about its mortality and morbidity rates; and you have lots of variability about what types of methods, you know, Zika was not originally known

to be sexually transmitted, but then was, right, so it is true, however, that I think that you could -- as you start building these models of how these things are spreading, you can use extensive computational tools and

(inaudible) tell you which pieces of information you need to know the most and that can direct your research efforts, or your surveillance efforts about which one of these parameters would it help me more to know more accurately than I know it now which is, now I don't know anything about it, or something like that. So even in the absence of lots of the kinds of data that you would normally have to, well, calibrate something about a typical influenza or measles or something, you can use models to direct the extra research efforts and the

surveillance efforts, and in what parameters, and in what populations, and in what locations do I need to know about this stuff.

DR. BIGGERSTAFF: I might add to that, that I agree with all of that, of course, and in terms of characterizing that kind of uncertainty for decision makers, it's useful to produce analyses over ranges of parameters and demonstrate to them that uncertainty, but also it can help them decide if they would make different decisions based on those ranges -- even if they're wide. But the qualitative characterization of that is such that decisions would be the same. That's useful in a sense, as well, I think,

DR. ROBERTS: I think for some of these infectious disease models, we need to get to the kinds of graphical displays that weathermen have about where the hurricane is coming. And the probability band distributions that everybody believes, although those -- there is not a single policy maker who understands the computational

models behind those things, but they understand the -- and we're not very good yet at presenting the kinds of policy-relevant uncertainties in our representations of the spreads of infectious disease. I think we need to do a better job of that. We're not doing anywhere as well as the 6:00 o'clock weather person.

DR. STRONG: So I think you're addressing the second part of that third question, which is how can we improve collection of information that can be used for estimates of these populations? There may not be an answer for that. Another point that hasn't been made that needs to be made is, the test kit manufacturers, because for blood donor screening there's a lot of work done in identifying since systemic specificity before a test gets licensed. For the tissue population, it's first of all, small in comparison to blood, and therefore doesn't generally meet the requirements of a manufacturer to make money, so they're unless inclined to invest in getting the kit licensed, but there's

also the problem of sample purity and the ability to measure the analyte that you're looking for in a sample from a cadaveric donor. So, this is a particular issue for nucleic acid testing, where a lot of the elements that occur in plasma samples post mortem interfere with the nucleic amplification process. So, the only thing I can comment on is that we need to encourage: one, the test manufacturers who do make money selling blood products testing kits, that they be encouraged to participate in also including samples from donors; and on the side of the tissue banks, that they also participate in providing samples. Many of them have banks of samples that could be provided to assist in the development of tests. We've had this problem with each new emerging infection that we've had to test for and it remains a problem, because it's hard to convince the test kit manufacturers. Are there any test kit manufacturers represented in the audience? One, one timid --

DR. PATE: (inaudible)

DR. STRONG: Yeah.

DR. PATE: (inaudible)

DR. STRONG: There you go. Maybe you'd like to comment on this problem, I don't know if you've been involved in the test kit manufacturing development, but could you just say a few words about that?

DR. PATE: Sure. My name is Lisa Pate, I'm with Roche Molecular Solutions. It is -- it's hard to not justify, but if you're not going to make money, it's hard to justify making a claim -- trying to get a claim and doing the work necessary for it. But, nonetheless, we do actually include cadaveric claims for most of our tests. Sometimes they follow the original licensure of the test, just because of the resources we have to do the testing, but we do look at that. We know it's important. None of us know who or which of us may need to be on the receiving end of tissue or organs and so we all have an interest in making sure they're as safe as possible.

DR. STRONG: And another relevant

comment is that blood screening tests are different than diagnostic tests, in terms of sensitivity and specificity, and for the organ donor populations that's been a bit of an issue in the past that because of the time constraints in moving the donor to transplant, a laboratory has to be used that is available and they don't always have the relevant tests to get the sensitivity and specificity that is necessary. The diagnostic tests tend to be different than the screening tests in terms of those parameters. Jay, would you agree with that comment? And Melissa would like to comment, too, do we have a microphone over here?

DR. FISHMAN: We have a question -- I'll come back.

DR. STRONG: Okay. We won't lose you. So this gets to how do we model when we're using different kinds of data.

DR. GREENWALD: This is Melissa Greenwald HRSA. The only other thing I'll add about what you're saying about organ donor testing

is that the policy has evolved to where most of it, and the availability of testing, most of the time organ donors are being tested now, not during the time that was assessed for the TODE study are being tested with donor screening tests, and it's much less frequent that donors are being tested with diagnostic assays although it does happen. And the other thing I'll add is just like in tissue donation, there's still a lack of any time to make any supplemental testing after a positive test result that ends up complicating interpretation of results for any of the studies that are done, just as Dr. Brambilla mentioned.

DR. BRAMBILLA: One thing to bear in mind too, is that the intent of the test when it's developed, the original HIV RNA tests, including BDNA, said on page 1 of the various package inserts, this test is not intended for diagnosis. They were monitoring tools to track patient prognosis, in patients you knew were infected. So that's the third category. And yet people use them for diagnosis routinely, in spite of that

warning. Now, the reason it's important is because, just to use the original monitoring test, which, of course, is now defunct, as an example, is that the boundary for calling something positive and, therefore quantifiable, the optical density, minimal optical density of.2 units was about nine standard deviations about the average optical density from a negative sample. So, you had a huge gap in there that mostly you wouldn't find people who had been infected for a while in that gap, because they had appreciable viral titers. It's just an example of a design that -- and yet it got used for diagnosis anyway.

DR. FISHMAN: Just to continue the discussion about the screening tests, when a new emerging pathogen comes in, like West Nile did years ago, and the tests are not available and you're using whatever tests are available, a diagnostic test, a screening test, the easier thing in the organ and stem cell population was a positive test meant an exclusion of the donor entirely. So, in some ways that wasn't so bad,

except for the fact that the test didn't work quite the way we thought they were going to work, because we didn't know the biology of the disease. For each emerging disease, it's a new paradigm that we have to figure out which test can be used, but in those populations, it's often a yes-no decision rather than a quantitative issue. It doesn't really matter how much you've got. It's like a little bit of syphilis, you described for your VDRL example.

DR. STRONG: I don't think we're making your policy decisions any easier. We have a question up in the back we don't want to lose.

DR. ZAMBRICKI: Christine Zambricki from America's Blood Centers. My question is two-fold. First of all, it was terrific hearing all the background on epidemiologic modeling. We do a lot at the policy front, and our members do, but probably not so much at the background behind those decisions, so I really appreciated hearing about the different approaches. My question is, the epidemiologic modeling is used to create

policies to provide for safety in our country, and I'm wondering, especially with these emerging diseases that kind of come and go, how much time is necessary in that life cycle to then make decisions about reversing policies, and taking away testing? And is that process of modeling different than the process of modeling when you're trying to make a decision for safety to start testing? And I'll give you a real-life example. Everybody knows last year there was a lot of attention to Zika and it was scary, and there was not a lot of information known, and so NAT testing was instituted, and across the country all blood is tested now for Zika. So, that was 100% the case by the end of last year. So now, in January we're looking at some data and 3.2 million donations have been tested and so far, confirmed Zika.001%, 34 cases out of 3.2 million. And 62% of those cases are in Florida, which was expected because of the vector. All of the rest of the cases outside of Florida are associated with travel and they're really southern states, except

one Massachusetts occurrence. So, that is a real-life example for my question. How, with that data and the fact that when the decision was made it was very unknown, how do you decide how much time has to elapse before you re-evaluate the decision? And is the process for deciding to make a policy decision to take something away, the same as the process as it is to put it in place when there's probably more risk at that point in time? Thank you.

DR. ROBERTS: Let me try on that one, because I would actually suggest, sort of theoretically as a health policy person, that the process for deciding to institute something versus take it away, is really, in fact, the same. You're balancing risks and benefits of doing something versus not doing something. In the first example, the decision is do I start doing this and in the second example, do I stop doing this? What I would say is generally different about the stop this decision is two things: one is, you usually have more information, so the

uncertainty bands around your estimates of what happens if I do "X" or what happens if I do "Y" are smaller because you've now learned more than when the air bars are sort of bigger. And I think that we see that many policy makers, not all the time, but we have seen in our examples of -- and the work we've done with both our state and the federal government, that there's a kind of a worst case scenario that drives the policymaker sometimes, that, even if it's very unlikely, if this really bad thing can happen, I don't want that to happen, so I'm going to make a policy that will prevent that really bad thing from happening. And the likelihoods of worst case scenarios in even the distribution, the description of worst case scenarios are generally more awful early on because of the wide uncertainties, than they are in the decision to -- so I would say that I personally think that the process really is the same, it's just that what you know about the disease and the bands of accuracy around what you know, is probably narrower in the decision to take

away.

DR. BOLLINGER: What if I could maybe ask a follow- up question about the -- does the biology of the disease we're talking about impact that, because, for instance, with Zika you have a relatively short incubation period, so you could look at the population, or sample those who received transfusions, even though they were screened and you could come up with probably some reasonable estimates on the risk of, in this case, of asymptomatic transmission. And you wouldn't have to do that for a long period of time because you generate antibody relatively quickly. You'd also be looking to see if your screening is missing cases either because the nucleic acid test is missing viremia or because the virus is in other tissues and can still be transmitted in other ways, for instance, in the urine or mucosa, so you may, I think it's important to see if you're getting transmissions afterwards. That's back to an earlier point and if you're looking at something like, with a longer incubation period,

you have a bigger challenge, because you have to wait longer after exposure to look for it.

DR. ROBERTS: I guess that's a question for me.

(laughter) We try very hard to represent the biology of the disease inside those models to the extent that we can. It's interesting that in our in-stage patients of HIV and Hepatitis C, our models are very biologically complex. Interestingly enough, our biologic model of influenza is almost laughably simplistic. It's a set of three numbers, an R naught; a length of infectivity; and, a death rate. That's it. That's our entire -- for all the work we did on influenza, it's sort of laughably simplistic. The biology of the disease can tell you again, if your model -- the more

detail you have in the biology of the disease, the more you can test various different questions about those kinds of different interventions or different testing schema or different sensitivities and specificities of different testing schema. I've always been a believer that you build as much biology into the model as you can, because then you get it -- now, it's harder to do that and especially on an emerging disease where you don't know a lot about it. We participate in the MIDAS, the Modeling Infectious Disease Agent Study grants by NIH, and early on, in some of those early predictions about Zika that were going on in the various (inaudible) centers, there was no representation of transmission

other than by the mosquito vector. Well, it turns out that's not right. The thing about models that I think is useful is the moment you figure that out, you can begin, it's just a trivial matter of programming, to sort of within a couple of hours figure out how that impacts what you're -- so I think that having a model -- it's a lot faster to learn how new data effects your decisions, than if you wait for the real world to show them to you.

DR. STRONG: I think there was another question. Oh, there we go, Ted.

DR. EASTLUND: Ted Eastlund. Is this microphone working. Ted Eastlund, retired tissue banker and blood banker from Minnesota, Wisconsin and New Mexico. I have a question, mainly to the first two speakers, but anyone. We're all concerned about the importance of the new viruses

from large scale pig and poultry farms from around the world and Asia, that can infect our blood supply and our tissue supply and we're acting quickly. It's very important to, but to what degree do the United States large scale pig and poultry farms, and we're the leaders in the world in that area, to what degree do our own farms like that create mutations, new viruses, influenza strains, that could enter our blood and tissue supply?

DR. BOLLINGER: Well, I've spent 37 years in India, so I know more about that than I do the domestic poultry and pig industry. One of the perhaps safety nets we might have here that doesn't exist elsewhere, is that there are presumably less likely chances for farmers who -- it's the farmers who recognize these outbreaks before we do. Their chickens start to die. So, in other parts of the world, unless you incentivize them, they're going to start selling those chickens as fast as they can, spreading the epidemic throughout the region, unless you pay

them to kill their chickens. So, we presumably have other ways in which we can monitor and incentivize people, I just don't know, but it's an issue around the world. If you raise the alarm for influenza in chickens and then these poor farmers are not paid, I mean, that's how you spread those epidemics. They will be putting them in the market as quickly as they can and spread the infection. So, I'd have to defer to others perhaps in this room about what we have in place to monitor the commercial poultry and then swine industry. I guess we don't have them together as much as we do in other parts of the world. They tend to be separate industries and one of the issues is the transmission between the species leading to the recombination, at least, to new viruses, but maybe others can comment.

DR. ROBERTS: Let me just say that from the point of view of modeling, we have not modeled the food industry yet, and how it does this. We did do an experiment that where -- when we were trying to understand the vector borne diseases

such as Zika and Chikungunya and Dengue, we did create a very computationally intensive model where we modeled in an area where we had lots of information about mosquitoes densities and the prevalence of the various different viruses in those mosquitoes and the number of mosquitoes expected to be in each square kilometer, we modeled -- we did an experiment where we modeled every single person and every single mosquito in an area to see if we could create rates of probably disease transmissions based on mosquito density, but from a much more highly detailed model. It took a long -- when you're modeling every mosquito, that's a lot of mosquitoes. But you could do the same thing in chicken production, in hog production. My guess would be you wouldn't get a lot more information modeling the actual chickens and pigs and things, as you would as simply modeling as a group, as a -- here's the number of chickens that are made in the United States and the number, and the different types of production facilities have X-number of different

kinds of ways of testing and doing things. My guess is that you could get there -- you could figure out how quickly something would move through the food supply, but I'm not aware that we've done that.

DR. STRONG: Well, we certainly have incidences of food-borne viral infection. The French case perhaps jumps to mind with HEV, so should we be also considering food vector transmissions?

DR. ROBERTS: Well, I think a lot of it, and I think it relates to a lot of the other questions that have been -- there's almost sort of a data liberation problem here, in that you were saying, for example, that many of the recipients of tissues -- there's no requirement to report certain diseases when they get them, when they're immunocompromised, and things. The same thing is true about finding all kinds of food-borne diseases and diarrheal illnesses and things like that. And part of it is that the data you need to make those rapid cycle decisions is often not

directly available to you. So, for example, some of those food-borne illnesses -- there have been a bunch of efforts, one at University of Pittsburgh, but in several other places, where just by monitoring the words that people are searching on Google, they can decide that there must be an episode of diarrheal illness somewhere and they get it quicker than they do at the CDC surveillance network. Some of those have missed fairly big things and some of them have hit them right on. We would argue that there's getting to be a real loggerhead between privacy and ability to get data that would help us make predictions of these things early on. I know, for example, we're doing a lot of work now modeling the opioid epidemic in the United States and trying to get data on things like the number of times the police departments have given out Narcan, or have used Narcan. It's really hard to get that information, because of privacy issues and jurisdictional issues and things. So I think many of these kinds of things that you could create almost real-time

monitoring systems for, we're running up against privacy issues about having that data legitimately available to CDC or research organizations, things like that.

DR. BIGGERSTAFF: One thing that comes to mind with respect to livestock is the United States Department of Agriculture certainly has epidemiologists and we interacted -- our CDC and our division in particular interacted with USDA epidemiologists early on in West Nile virus, in no small part because while West Nile virus certainly causes severe illness in humans, it also does in horses. In fact, West Nile virus was early on recognized by veterinarians, both at zoos and with horse work. Maybe it makes sense to have USDA epis in the room for discussions related to zoonotic diseases. Are there any here? (Laughter) It's a thought. Again, statistics guys. That's maybe not a bad idea.

DR. BOLLINGER: Yeah, I think our only -- just quickly -- raise at least a question about in my last couple of slides, it would be

interesting to see what happens with this issue if we start transplanting our microbiomes a little more frequently and -- because antibody-resistant bacteria in the food industry is going to be a much bigger issue in that setting as well.

DR. STRONG: Just to make a political statement that the need for a biovigilance system in the United States has been around for a long time. There is a question up here?

MS. HECK: Thank you Mike. Back from the olden days, we had a virus that affects tissue a lot, and that's Hepatitis C. Ellen Heck from UT Southwestern -- and I was wondering now that we have drug therapy that is -- at least appears to be eradicating this disease -- our hepatologists tell us that it's 100% effective in many, many individuals. So as we forecast policy making for the future, will we be able to add these people back to the donation population once they've been treated and, for some period of time, shown eradication of the virus?

DR. STRONG: I'm not sure who answers

that question.

(Laughter) That's the FDA people, they are all ducking.

(Laughter) Yeah.

DR. McCLURE: This is Michelle McClure from FDA. I think one of those -- that's a tough question to answer at this point. It's a matter of time and seeing what we learn from the disease. We know that testing liver for a specific disease, or testing blood for a specific disease, what we've learned with some other new emerging, recently emerged pathogens, is that sometimes viruses hang out in other tissues and we think that the disease has been cleared from a person. I think it's just a matter of meeting time and gathering adequate information to know that there is no longer a safety concern that we have to worry about.

DR. ROBERTS: Let me just add that it took a long time, for example, for the transplantation community to be willing to transplant a Hepatitis C positive liver into a

Hepatitis C positive recipient, even though theoretically, you say, gee that makes sense. The same might be true of an HIV positive donor into an HIV positive recipient. And so when you ask, now that we have the direct acting anti-virals that will theoretically eliminate Hepatitis C, does it make sense to take the people that have Hepatitis C, which are 3 and 1/2 million people in the United States, if they've been treated and their virologic response is completely suppressed, could that person's liver be donated into a, or partial liver be donated into a, Hepatitis C negative person. I think that if you're going -- we know enough about Hepatitis C and we know enough about some of those other viruses, that you can do quite a bit of work to see if there are any legitimate viable virus particles in that liver, and I guess, my own personal feeling would be -- I know that rules would have to change, but if you were to ask a recipient, a potential recipient, who's on this really long waiting list, and says "Okay, we have this liver that happens to be from

somebody who used to have Hepatitis C, but it got cured, and it's gone, would you like this liver or wait another X-years, or however long it takes, depending on what DSA you're in, "I'd be willing to bet people would say "Yes, I'll take that liver". I'm sure that it will take a while for the rules and regulations to go there, but I'd be willing to bet that people would take that.

DR. FORSHEE: My name is Rich Forshee. I'm with the FDA Center for Biologics, Office of Bio Statistics and Epidemiology. I just wanted to mention that tomorrow morning's session is going to spend a lot of time discussing how to think about the benefits and risks, and what those trade-offs look like, what sorts of data that you need, and so I think some of that question -- it's not an easy question to answer, so I'm not promising an answer tomorrow, but tomorrow morning we will be having a discussion about some of the things that you need to think about when considering what the benefit risk balance looks like. So, thank you very much for the question.

DR. STRONG: We're running real short on time, but we'll take one more quick question.

DR. SCHULTZ: Dan Schultz, Chairman at AATB LifeLink Tissue Bank, medical director. Just one comment -- we know that predicting in tissue donors, post mortem samples is very difficult. But history has been in the past very relevant. So, for example, if you take something like Zika, we already have a year-plus of data; we have current recommendations as to look, if they've got a diagnosis in six months, we know there's a cohort of people who clearly have Zika virus at some level, because there's no current tests. It's been out there. It's been in organ donors -- it has to have been. The fact is, there still have been no reported incidences of transmission. So, we also have to look at the past and there are no good ethical ways to actually test for infectivity in humans, currently. And so the past is very relevant, and I agree that predicting for the future is difficult, but we do have a good -- well more than a year of data that at least says

that under our current parameters, we haven't seen anything happen. And that's where time is a benefit to look back.

DR. STRONG: All right. It's time for the break. So, thank you everybody for participation.

(Applause)

SPEAKER: We'll start back at 10:55.

(Recess)

DR. MCCLURE: Okay, let's start the next session. All right, so this next session is designed for us to have an opportunity to talk about the potential for transmission of donor derived diseases by HCT/Ps and moderating this session will be Dr. Matt Kuehnert from CDC.

DR. KUEHNERT: Thanks, Michelle. Thanks for the opportunity to make some broad overview points. I have been given a bit of a daunting topic to discuss the history of infectious disease transmission by human cells and tissues. I'll leave specifics to the other speakers in the session except to give some examples to illustrate

some points.

So first of all, why care about history at all? Those who don't know history are destined to repeat it. It's attributed to Edmund Burke. I am not sure if he actually said that. I guess in the irony of trying to record quotes in history and the next question is what is history regarding a disease transmission event and this was touched on in the first session. What you need for history of an event is the risk of an event occurring, the event actually occurring given the risk and then that the event is detected with either an adverse outcome or not and this is where commonly you don't have the recognition, at the clinician level but even if it is detected at the clinician level, it has to be reported somewhere, the public health authorities or for instance to the tissue bank and then public disclosure of an event, such as a publication to disseminate information.

If any link in that chain is not connected, we don't know about it and say it

didn't happen so with history, starting from as far back as I could reach, there were these twin brothers who were Saints Cosmas and Damian, they also happen to be physicians and they were Christian martyrs. I guess one of their surgeries didn't go so well.

Well what this one shows is an actual limb being transplanted in the third century. Since it was a limb, it technically wasn't an HCT/P, it was composite allograft and should have been overseen -by HRSA, but anyway, we'll let that go. We also don't know if there was any surveillance on that outcome. You can see that there was some angelic surveillance but we are not able to access the data.

So we only know what's documented and we can say that risk exists but it's not well quantified and focusing just on donor derived infections and not environmental contamination and those sorts of things, there have been several notable transmissions that illustrate the issues concerning those investigated by CDC.

I just listed a couple of them here. The first one was one that I became involved with which was a candida albicans transmission in 1996 when I was an EIS officer due to inadequate disinfection of the valve. I am going to be discussing hepatitis C, a virus transmission and then there are a number of bacterial transmissions including strep associated with tendon, clostridium sordellii also associated with the tendon, cornea transmission and mycoplasma hominis, which is the newest transmitted pathogen that we have investigated that is associated with the amniotic membrane.

Just as a general sort of average in terms of CDC investigations, we see about five suspected tissue transmissions per year. There in just the last few years we looked at it and it sort of runs the spectrum between bacterial viral, fungal, mycobacterial. I have not seen many parasites or prion disease that's suspected to be transmitting and then two of these have been confirmed so a fairly low number compared to what

we see with organ transplant and blood transfusion, and then of course there are those that have theoretical risks that, the Zika virus being the most public right now and I'll let others speak to that pathogen later on in the workshop, so how do we know that there is any risk at all?

We do public health investigations at CDC. We support and assist upon invitation based on reports from any source and they tend to be pretty varied, state health departments are our eyes and ears but also other agencies, tissue banks, OPOs, clinicians are very, very important on the ground in terms of sentinel surveillance pathologies, particularly on autopsy when those are done. Laboratory staff, even patients and their families. There is also, of course, FDA reporting but there needs to be a donor recipient link made in order to raise suspicion that it might be donor derived and sometimes lawyers tell the story but most often settlements are totally confidential so we don't hear from that realm very

often. I just wanted to make the point here, this slide is from Dr. Eastlund, making the point that most transmissions through tissue that are reported are associated with unprocessed tissue and you know, of course, this is just numerators and so it's very difficult to make any kind of a rate calculations so you can see again quite a spectrum of organisms, especially with fresh, frozen or cryopreserved tissue running the gamut with viruses, herpes viruses, HIV, HBV, HTLV.

Rabies is a fresh artery, again, this is not technically in HCT/P, this is a vessel conduit that was used to connect the liver to the recipient that was rabies infected and we see CJD that is associated with the cornea, fungi, mycobacteria. So a large spectrum but with the common factor being fresh or frozen or cryopreserved tissue.

I wanted to illustrate, you know, some of the important points about transmission with this event. This was back about 15 years ago in 2000 and the issue being communication so what

happened here is that there was an infected donor that was not detected because they were in the window period for hep C because what happened was although a diagnosis was made in the organ recipient, unfortunately no one told the tissue bank and so the tissues were distributed and implanted so it gives you a little bit of a natural history of what happens when the donor is infected with hep C and tissues are implanted, who gets infected, who doesn't.

So there were six organs -- well actually, just to back up, there were 91 organs and tissues recovered, 44 transplants into 40 recipients. Of those, there were 6 organs, three died before being able to be tested, three were shown to be infected, there were two corneas -- cornea transplants. One had been previously infected with HCV, the other was shown not to be infected and then there were 32 tissues.

Of those 32 issues, four had been previously HCV infected. Interestingly, there were two recipients that were not available for

testing. They couldn't find one of them, the other one the hospital just couldn't figure out where the tissue went, they knew it went into someone but they couldn't figure out who it went into, which is a problem.

And five recipients acquired HCV and the important point there is that all three who had bone tendon bone grafts that were not irradiated were infected and there were 21 who did not have transmission including 16 who had irradiated bone, and two skin recipients. So again, the theme of processing seems to prevent transmission.

I wanted to move on to a more recent HCV transmission where a lab error was the problem. So in 2011, CDC was notified of two kidney transplant recipients,again, the organ recipients tipping us off, in Kentucky, who tested positive. At the time of donation, the organ donor had tested negative for HCV antibodies. There was no NAT testing for organ donors at that time widely. The donated organs included two kidneys and one liver and there was donated tissue that consisted

of 44 grafts. The donor serum, as I said, was tested negative for antibodies by the OPO. The serum was tested by the tissue bank. It tested negative for HCV antibody and NAT so what happened here is that there was mislabeling of the specimen that led to a false negative HCV NAT result and retesting later confirmed that the donor was HCV NAT positive. So at that point, there was a race to try to figure out what were the tissues, what's the status and, although in this event the communication was quite rapid between the transplant centers, the OPO and to the tissue banks, unfortunately some tissues had already been distributed and were already implanted.

So as I mentioned, there were 43 musculoskeletal grafts, 15 implanted across nine states that had been treated chemically and by irradiation. There was one additional tissue which was the cardiopulmonary patch which was treated with antibiotics per protocol, no irradiation, chemical treatment, and so we began to notify surgeons and requesting testing of

recipients.

So through all this, it was determined that there was one HCV transmission and this was unfortunately the cardiopulmonary patch implanted into an infant in Massachusetts. The other 15 grafts had no evidence of transmission on testing the recipients. The other issue I wanted to highlight is that how long it took to locate an implanted tissue. It took -- so this is the number of days from CDC notification of physician contact, or the facility to identify who the physician was, and also identify the patient, and it took between a week and three weeks, a minimum of two weeks to do that and it took even longer to get the patients tested and there were some interesting stories there about why there were some problems locating recipients but the bottom line is a lot of hospitals do not have tracking systems for tissue.

So these are two sort of anecdotes right? What we'd really want to know is how often do these events occur and there have been studies

on this using modeling. This is a slide put together comparing modeling results for risks between organs, tissues and blood and for tissue, the risk -- let's just focus on HCV is about 1 in 42,000 using serology alone. If you add nucleic acid testing to that, for HCV it's reduced -- the window period is reduced by 90 percent and the risk is somewhere around

in 420,000 and that's for individual NAT and that is somewhat comparable to the one in 1. 2, 1. 5 million from any pooled NAT associated with blood.

But even with that, if you do the numbers on what we think the number of transfusions and the number of tissues implanted, there is still going to be infections that are transmitted, even with that very small eclipse period but we don't see those very often. So what can we do? So this is a little bit complicated and really beyond my purview but I thought about some of the ways that we've tried to gauge risk in the past.

One, there was a workshop that we put on back in 2005 and one of my colleagues, Arjun Srinivasan added all published cases up and divided by the number of tissues distributed and said this is the rate of transmission possibly. That's been often quoted -- and I think maybe misquoted. It's simple, it's good, pretty simple and provides an estimate floor but it must - - it's probably much more common than that because all the layers that I mentioned about what it takes for something to be published. The other is, I'll call this, the Strong method. My colleague, Mike Strong, who has been involved with these studies to use sensitivity modeling for screening pathogens so you look at the characteristics of the test and the window period and try to estimate how many might slip through, but the problem has been mentioned before.

There is a large discrepancy between predicted and observed, for instance, for HIV, transfusion transmission, we'd expect about 30 times more cases than what we see annually. The

other approach, one of our statisticians, Matt Sapiano in our division in CDC has talked about incorporating donor screening, tissue type, and processing transmissibility to sort of use a reassurance or wax one approach to look at the extreme value distribution of what might happen and then look at the probability of not seeing a case over a certain number of times so how long would it take for you to expect to see a transmission and then try to calculate on what the issue might be if you don't see it?

So what are some models on maybe how to improve surveillance? This is an old slide set but that's okay. So better surveillance is the key and for organ transplant, we have the disease transmission advisory committee and some of the audience has been involved with that. Jay Fishman was very involved in starting that effort and I think it's worked out very well. It's been incorporated in the policy. They make a determination on likelihood of transmission, interface with public health authorities, CDC is a

member and we really thought, what was not thought to be a problem, turns out is a problem so there were no -- barely any cases at least, early on and then as of 2009, there were about 150 cases of suspected disease transmission through organ transplant reported and now there is about 300 so it's -- some of it is probably not relevant but a lot of it is.

We've definitely seen a lot of repeats but also some new pathogens that have come up. Balamuthia, microsporidiosis, a number of different fungi, so there has now been enough data to try to estimate for organ transplant and perhaps.2 to.5 percent of recipients have unintended disease transmission which I am sure is much higher than either blood or tissue but it is a number that could be arrived at with surveillance. Just quickly I want to go over some comparisons between blood, tissue, organ and hematopoietic stem cells just to give you a sense of differences in tissue tropism. I mean the bottom line is there isn't a lot of tissue tropism

for a lot of these, perhaps exceptions being syphilis and parasites -- parvovirus I think is just an artifact of it not being detected. It likely happens, as you can see here for tissue, parasites are a little bit hard for them to get into the tissue that caused transmission and survive particular processing. I want to close with a couple of things on how we might want to access risk possibilities. The WHO has developed a resource through Project Notify, compiling references on disease transmission through organs, tissues, cells and most recently blood was added so there is a website notifylibrary.org. It's searchable and it includes both adverse reactions and errors that have been reported as publications or that have been reported in the so called grey literature to the public health authorities so this is a resource that can be used.

I am going to skip over these. Zika is going to be covered I think later but one, our most recent investigation involved Mycoplasma hominis. It's a GU tract organism. Again these

two clinicians noticed surgical infections associated with amniotic tissue implants that were linked to a common donor. We did a multistate investigation and found the M. hominis matched the unused vials with these clinical infections and also I think of great concern is that in five of 27 vials, the final disposition of those vials could not be confirmed so again, traceability is an issue still, I think, in facilities and that hampers investigations.

So in conclusion, many infectious pathogens can be transmitted through HCT/Ps including viruses, bacteria, parasites and prions, the risk of transmission is variable, related to pathogen tropism, tissue type and of course, tissue processing and preservation also.

Without surveillance or other donor derived infection monitoring, it's difficult to quantify risk and you need both the numerator but you also need the denominator and it's been difficult to get that data. We know how many tissues are distributed, tissue banks are very

good at having that information but once it gets into the hospital or the outpatient clinic, it's -- that is information that we don't have and perhaps nobody has in some cases so when traceability is incomplete, investigations are difficult.

Modeling may shed light on risk though but data has to be driven by research. I'd like to thank those who helped me put this together and thank you very much. Next, I'd like to invite Ted Eastlund to the podium. He is going to talk about infectious diseases transmissions but conventional tissues and he's going to tell us what conventional means and I just wanted to say that he's our infectious disease physician emeritus and tissue banking and we are glad to have him.

DR.EASTLUND: Thank you very much. Can you hear me in the back okay? Good. Since around the early 1990s, in my job as tissue bank and blood banker, I have been paying attention to the diseases transmission cases that happened in the United States and I'll show you a catalog that

lists those.

I'll show you in a catalog form, which diseases have been transmitted by which tissues and where it looked like the failures were also so we'll cover the documented case of transmissions, types of pathogens, the types of allografts involved and I'll emphasize again the difference between the so called viable tissues versus the non-viable tissues and what we can do with them.

The age old discussion about the multi-layer approach that is essential in reducing risk, or selecting a safe donor and reducing the burden, which we have been doing for years and the effects of processing steps on risk reduction and burden reduction and disease, transmission risk and finally a tiny bit about bio surveillance and I'll remind you that I am starting 15 minutes late, that I started with 87 slides last week, down to

on Friday and 34 yesterday -- two days ago and I timed myself at 19 minutes and I am almost half done so don't blame just me for your

late lunch.

The so called conventional tissues are listed here, except for corneas, which Marian will take care of next but from the deceased donor, that includes bone, ligaments, soft tissues, skin, heart, veins, arteries, dura mater and nerve conduits. These, plus live donors, we don't have much femoral head donations as live donors in the U.S. anymore but in the rest of the world there is, amnion and viable nerves.

Okay, for years we have been recognizing that there might be a difference in risk that seems natural when you look at the viable fresh frozen types of tissues versus the non- viable tissues that can go through extensive disinfection and sterilization. Here is a list of the tissues that we distribute right now.

On the viable side is refrigerated cartilage, fresh refrigerated skin, arteries, fresh nerves, one case of a disease transmission through that, refrigerated corneas, cryopreserved heart valves, veins and conduits, fresh frozen

articular cartilage, using some DMSO, unprocessed femoral heads, cryopreserved demineralized bone with stem cells added which are live, cryopreserved amnion with stem cells -- not cryopreserved but sort of cryopreserved amnion, solutions to -- that are added to spine fusions as the source of mesenchymal stem cells according to their advertisements, and also this compares to the ones that we can process well and that make up numerically, the vast majority of the tissues that are distributed, namely bone and tendon, ligaments, acellular dermis, dura mater, decellularized hearts coming up and nerve conduits also, ear ossicles, and pericardium.

I guess we should not talk too much in detail about some of the viable tissues that are frozen in the past, even some of these were used for growth factors and amnion for wounds and a source of growth factors. Amnion, decades ago, for treating Tay-Sachs and Neimann-Pick's that gave temporary relief only. So a long history of using cells and tissues that have metabolism

preserved to produce growth factors but they can't be sterilized compared to the non-viable -- we better hurry through this.

So let's go over the disease transmission, just to emphasize about the transmission rate of the frozen, untreated and oftentimes viable tissues, they should have a very low risk when we do our job well but there is still a predictable low rate of transmission.

On the other hand, the heavily processed, disinfected, and so called sterilized, at least irradiated tissues, show you have such a reduction of bioburden, plus irradiation before and after that so I think it approaches almost medical device type sterility in current large, large tissue banks anyway in the U.S. so there is a difference between the two that has widened in the last 15 years as processing and sterilization has become quite sophisticated.

I want to go first through just showing the slide about the fatal cases. This is a list of all the fatal cases that I can come across.

First of all, CJD over 200 cases worldwide, a few in the United States, always -- almost always one producer in Germany using methods with pooling of dura during processing and possibly not much donor screening, just at the same area that the pituitaries were being collected at autopsies and over 200 kids have received growth hormones from that and gotten CJD -- it's about an equal number of a couple of hundred from dura and a couple of hundred or so from not just growth hormone but also some other hormones from pituitaries so we have had two cases or several cases in the U.S. and one in Canada and this is a surprise because it's not always just lyophilized dura but this is a different type of processing of the dura, which is excellent processing to get rid of bacteria and viruses. The

(inaudible) it included non-pooling, number one, it also included acetone, sodium hydroxide, that's supposed to have an impact on prion transmission, a number of

good strong treatments and yet there are two cases out there that seem to be transmitted by that product also.

Next is rabies, with eight cases from cornea around the world, an iliac artery case, also some femoral heads and tendons, some famous cases of HIV transmission about five, possibly an old article, four more but it's in German and it's never been -- it's never had a chance to see if it was frozen or was it freeze dried. A letter said freeze dried, the article said frozen and only the letter was in English.

One famous case in 2010, a young man with acute sepsis on day three after a fresh, refrigerated cartilage. Here is the list of the bacteria transmissions that have been known, and fungal and tuberculosis, some are historical, TB 1954, and old heart valves on the bottom right there. I made this into the red ink as truly infected donors which he mentioned earlier about the group, toxic shock case but the diagnosis by

the emergency room physician, by the autopsy pathologist and the tissue bank director were incorrect and it took bio surveillance, that is reporting an investigation, to go back and do the testing to prove what went wrong but also how to prevent this in the future.

In the brown are cases of bacteria that are from the donor, so they are donor derived but the donor was not infected. This is from translation of the intestinal bacteria, there is a very sensitive lining on the gut that even with severe ischemia, you can get some bacteremia. Well once you die, they flood the rest of the body and that's why we have short time intervals after death that you must collect the tissues and these are ones that are donor derived but they are really acquired during time of death or during recovery and you can see all the lists here. I won't read them all right now. The slides will be available, I am sure, some time. Fungal, we had talked about the heart valve incident, a very good case report on that and fresh corneas too.

These are true derived viruses, derived from the donor, that had been reported and really worked up well. HIV from bone and tendon, HCV from bone and tendon, and all of these have really interesting stories so we should take three or four hours to talk about these.

Cryopreserved saphenous vein, in the case that Matt showed, that was reported to a processor between the time of donation of the organs and a long time later when a tissue bank processed the tendons and that never came to light until during the investigation because the tissue bank said, well the tests were negative, they couldn't have been from us but not the other tissue bank, they thought about it.

Also the cryopreserved cardiopulmonary patch, and HBV in the old days, and the cornea and also heart valves. I investigated that. Other ones included the rabies we talked about, the cornea and the fresh artery, talked about the CMV, it took a long time to prove and that was actually transmitted from fresh skin transplants and it

wasn't the blood transfusions they got. The freeze dried dura, we talked already about. Herpes simplex from corneas, EBV through a live donor, a father donating for his son who had a nerve injury in a flail arm and he gave his nerve from down by the ankle and also gave him EBV and mononucleosis. The HTLV one, they didn't test it and it was transmitted by a fresh frozen femoral head.

Let's look at sources of contaminations. Here's the catalog of what I say with the causes. Number one, this diagnosis of infectious cause of death, I give some examples. Another one is the group B sepsis, donor screening, tissues, donor testing for the infectious agent because the test wasn't available or they just didn't do it. In a number of viruses, insensitive donor testing, using donors with known infection, hepatitis B with heart valves, almost all of them had antibodies but there was at least one that was negative and got the disease.

Failure of the health authorities to

prohibit importation of known infections allografts, the U.S. acted fast, Japan didn't and that's where most of the cases were.

100,000, apparently, uses a year in the heyday of dura in Japan. Failure to -- use of contaminated fluids, HBSS solution was contaminated by Ochrobactrum anthropi and caused five cases of meningitis because of it when it was used for dura patches, contaminated allograft from the processing environment and (inaudible) test tissue allografts containing residues of antibiotics and interfering with the final testing. There were quite a few cases like that and the failure of a simple human error of not employing their terminal sterilization. They would have tendons that were used but they didn't do anything to reduce that. They just gave terminal sterilization and they forgot to do it on a case and there two cases reported in an MMWR because of that.

Let's go quickly into donor screening. I'll just list them. What most people forget is

that volunteer donors are safer than paid donors,
to 50 times increased risk of markers and disease transmission so luckily we have volunteer donations mainly to -- donor history screening and that's variable when you talk about especially what happened in the last four or five days of life -- that's the hardest part to document. Risk behaviors are carefully screened for. A physical exam takes place, there was blood testing and microbiology testing of recovered tissues takes place too.

Now microscopic examinations of tissues were a little different, both modern biopsies take place and sometimes they examine the heart and autopsies. We'll go over the processing, which is really an important step in sterilization and lastly they had surveillance and so this is a Swiss cheese model where each of these reductions, step reductions, I listed about

of them are imperfect barriers and if you stack one next to each other, it would be exceedingly rare that all the holes would line up

and yet it happens and so you need to have many holes lining up. Failure in more than one spot, except for that one case where they did terminal radiation with hardly any other processing, you need to have a lot of things lining up and multiple failures, usually, than most of these cases.

Just quickly, I just mentioned that -- recovery biopsies are done at some tissue banks and authorized the staff with certain circumstances that decide to do biopsies and a series of 560 over five years showed that 1. 3 percent have significant malignancy or sarcoid granulomatous disease, that's 3.6 per 10,000 donors. Now that may be important for viable, fresh frozen tissue but the bulk of it is processed and so it has no added safety benefit to the processed, disinfected, sterilized tissues but possibly others.

It does help make the recovery process more efficient and it allows saving a lot of donors by doing a biopsy to make sure that the

donor is okay, so what's the effect of processing. This survey in 2013, U.S. tissue banks, one of the biggest ones wouldn't participate, three others wouldn't participate at first but eight to nine months later, they participated verbally and one happily took the whole test, the whole survey.

This is a study that Theo de By, Martell Winters and a guy named Mike Strong helped out and so it's not just one person that gets blamed for the data but you can see that almost all of them do significant decellurization steps, alcohol, and antibiotics of different types. This is one common -- I forgot to take off one other word there but spiking, to validate your process and it shows the bacteria that was spiked and what the log reduction was and if you simply add them up to the right, you get between 10 and 20 log reductions which is a nice reduction, and on top of it, all except one of these has irradiation while it is in the package. Now it's low dose so it doesn't have a big effect on the bone and tendon but that's really effective. The other one

has a radiation also to reduce the bacteria before processing so you're starting out at zero bacteria basically and so you still add up to have a terrific log reduction.

Another one here by a different bank used -- came up with the same thing, 10, 11, 12, log reduction. Spiking the viruses and documenting the log showed equivalent also with these model viruses that mimic the viruses that we work with or the viruses themselves so it demonstrates a very good log reduction bioburden which you have dedicated yourself to do even without processing so you add all those together and you end up with a thoroughly safe product.

Now lastly, I wanted to mention about virus surveillance because that's the one area that's truly as important as each of these steps because the number of cases have brought the light problems, for instance, bio surveillance ended up with organs, suddenly, they are realizing the complexity of encephalitis and have learned many new (inaudible) and such that have been

transmitted in case that they might have been accepted before and then we find out now, from tissues, back in 2002 that merely hypotension and redskin is enough to reject a person because the risk of bacterial sepsis. It's not always antibiotics and in that case, we have this toxic shock like syndrome that transmitted through tendons was one of those cases with initially -- on the day of death, based on hypotension was still red from its previous admission in emergency room too so the problem is that these diseases pop up late and this is one of our last slides and as you know, it's up to 25 years for CJD for dura but most of them are a few weeks to two to eight months for documented, disseminated tuberculosis and this is what we say all physicians need to know and how many of us know it so it's a daunting task to -- if you asked anyone, any doc out there what's the risk of transfusion, they say -- they come up with hepatitis and HIV. Well if we can at least have -- we do have that degree of education but I think we need more dedicated educational

efforts so that not just the orthopedic surgeon who will see them up to a year later but the other docs that take care of them for 25 years and unfortunately I have to use the word 25 years, need to know the presenting signs and symptoms to be able to report them to FDA, tissue bank and all the people involved in order to trigger what's so important and that's a root cause analysis, corrective action and applied not just locally but applied every place.

So in summary, risk is reduced by carefully performing a multi-step process to select the safe donor and to reduce bioburdens.

Failures will occur at many of these steps but because of the many, many steps, most of them will be caught and are caught at various stages. Today, bone processing at least has reached a high degree of safety. The risk depends on the type, and the frozen viable

(inaudible), the risk is greater in those and so for those, I'd say we need more improved process control,

QA, clinical safety and efficacy of studies, virus surveillance and clinical follow up are important and warranted for especially these as well as the others.

The trend for heavy disinfection, for terminal sterilization, for the other banks in the country and around the world should be highly promoted and yet it's kind of a slow progress. Virus surveillance still needs improvement so all cases are identified and new types of infections are emerging as we know. The Zikas and the Chikungunya need close surveillance so we can act quickly and programs are also needed so that they have clear indications for allograft use, like blood, that's evidence based and should be peer reviewed and monitored against the indication. That would help us identify or use it properly and reduce the risk to the patients. Thank you very much.

DR. KUEHNERT: Thank you, Ted. Next we have Dr. Marian Macsai from North Shore

University and he's been very involved with EBAA to talk about infectious disease transmission ocular tissues, thank you.

DR. MACSAI: Thank you, Ted, to Matt and the organizers of this interesting conference today. I'll be speaking to you about infectious disease transmission from ocular issue transplantation and I have no proprietary or financial interest in any of the products we'll be discussing but I would like to thank Jennifer DeMatteo from the EBAA who did help put together this talk.

So corneal transplantation is a little bit unique when compared to some of the other tissues we are discussing. It's performed within two weeks of harvest, the tissue is avascular, disease transmission is rare, adverse reactions are tracked initially and again, at three to six months post transmission and as Matt alluded to, in cases where HIV positive tissue has been transplanted, the cornea recipients remain disease free, so what is actually happening for patients

is that the surgeon typically requests a cornea and it appears in the operating room.

There are 134 corneas transplanted daily in the United States based on 2015 statistics. Corneas are used for a multiple of different procedures from full thickness corneal transplantation which was dura graft 20 years ago to partial thickness corneal transplantation, which is now the norm.

The most common from our recent statistics being endothelial keratoplasty in the United States, scleral grafts and long terms present rations are also done as well as scientific studies. Our data from 2015 reveals that 130 -- almost 131,000 whole eyes and corneas were donated of which 79,000 corneal grafts were used for transplant. Over 25,000 were exported outside the United States and over 26,000 corneas were used for research and education.

So let's look at ocular infections. The ocular infections we care about are endopthomitis, infection of the whole eye, keratitis, infection

of the cornea, scleritis, infection of the wall of the eye and in each of these cases, the disease presents three to fourteen days after the inoculation and it may or may not be from the recipient. The way we determine this is we do cultures of the fluid inside the eye and we did it to match the culture results that are found from the donor to the mated ocular tissue transplanted into a different patient.

One of the issues with ocular infections is that many come from the recipient's flora. The eye is not sterile into which we are transplanting the cornea. Our data reveals that the incidence of endophthalmitis is 2. 8 per 10,000 cases in the EBAA statistics and this ranges from five to 26 cases per year, we'll look at those later.

Now, Ted talked about rabies and in fact, there are 11 reported cases or rabies transmission, only one, the top, being in the United States in 1979 and this is before donors were screened. Imputability is determined by the temporal association of the illness a lack of

other exposure and of course, examination of the cornea discs for rabies virus RNA by PCR. As I said, there has been one case in the United States since '79, 10 cases outside the United States.

CJD, the diagnosis of CJD is made by basically brain biopsy. It's confirmed by a test of the corneal tissue or optic nerve. The problem for corneal transplants at today's date is that brain biopsies take too long to be processed. By the time the brain biopsy is processed, the tissue has been transplanted. There is one proven case of transmission in 1974 and then there are nine additional cases that have been reported as probably or possibly due to corneal tissue. In a CDC study, it was interesting that sporadic or coincidental CJD unrelated to donor tissue is expected to occur in one corneal recipient in the United States every 1. 5 years.

It's unlikely that the possible and probable cases were due to the corneal tissue and that there are additional unrelated coincidental cases that probably remain unreported. It's our

hope that EBAA's screening minimizes this risk of transmission. Hepatitis B, there have been two reported cases of presumed transmission in 1995. Dr. Kuehnert discussed these a bit. Serology was confirmed as acute HBV infection eight to 14 weeks after corneal transplantation with no other risk factors or exposures. Identical donor or recipient subdeterminants or antigenic subtypes were determined in these cases. Since that time, there have been no reported cases of hepatitis B transmission.

For hepatitis C, there are no reported cases of transmission through corneal tissue. There is an interesting case of a positive donor that resulted in positive seroconversion of five organ recipients. The two corneal recipients did not have positive seroconversion. One of them was positive for hepatitis C before transplant. The other did not seroconvert, yet both hepatitis B and hepatitis C are contraindications of donations of corneal tissue.

Herpes simplex is a much more

complicated issue. The incidence of this audience being infected with herpes simplex is over 90 percent. When we do transplantation, the act of surgery, the use of steroids can reactivate herpes simplex hence it is a difficult thing to demonstrate transmission of the disease yet it has been transmitted through the detection of DNA by PCR in one donor and in this case, the genetic characterization of the herpes simplex virus type I was isolated from the donor before and after corneal transplantation in the recipient, demonstrating transmission through transplantation but it is, as I pointed out, a very complicated situation due to the fact that recurrent disease can be activated by the surgery or the steroids we use routinely during transplantation.

Other viral infections, there are many, CMV. Well again, this is a situation where a virus can be reactivated by surgery and steroids but there is one known case of transmission where there was a known seronegative recipient who sero converted following transplantation from a known

seropositive donor with no history of blood transfusion or prior febrile illness.

HIV is obviously something of great concern to all recipients. There is a host of information regarding HIV transmission through ocular tissue. In 1987, Pepose reported four corneas from two donors who were serial tested positive for HIV antibodies without seroconversion and the recipients and Schwartz described sero conversion in organ recipients but not in three corneal transplant recipients who received tissue from HIV infected donors.

And then again in '92, Simonds reported that all four recipients of organs and all three recipients of unprocessed bone who were infected with HIV one but 34 recipients of the tissue to corneal recipients tested negative for HIV antibodies and this donor was in the window period as we've talked about after infection, prior to detection by testing.

Some other less commonly talked about infectious diseases include syphilis, ocular

syphilis presents with iridocyclitis scleritis retinitis, optic neuropathy -- there have been no cases reported of transmission via ocular tissue and this is because the cornea does not have a blood supply, it is an avascular tissue and syphilis requires serum to survive.

Ebola, a rapidly emerging infectious disease. Ebola is a contraindiciation to donation but we all know that Ebola virus has been detected in the aqueous humor of the patients who have survived this devastating infection, even 9 weeks after the clearance of the viremia.

Zika virus, again, never transmitted through transplantation but of great concern to the public and great concern to the ophthalmic community. Zika virus not only causes genetic deformities but in those who survive the infection, there has been reports of nonpurulent conjunctivitis, bilateral interior uveitis with keratic precipitates, aqueous humor has tested positive for Zika virus RNA by means of real time PCR and one case of bilateral posterior uveitis,

PCR was positive of the vitreous humor.

So this is an expansion of Ted's table, looking at infectious diseases transmitted by the cornea and these are those that have been reported as having been transmitted and the ones that are blank have not been reported as being transmitted. Where did all these numbers come from and how are we tracking this?

Well the Eye Bank Association of America has 100 percent of US eye banks as members. This organization credits eye banks and puts forward medical standards twice a year that require the tracking of all recipients and seeking three to six month follow up on all recipients and this is part of the accreditation process.

The outcomes are then reported to an online adverse reaction system. Here is a graph demonstrating the infections per 10,000 corneal transplants and in red, you will see endopthalmitis, in blue you will see infectious keratitis, these are localized infections, not systemic diseases. When we looked at the

endopthalmitis, we can separate it by different pathogens as you see here, color coded in the slide.

We tracked this very closely and one of the things that we will be looking for always is infectious disease transmission and over the past few years as endothelial keratoplasty or partial thickness corneal transplantation has become more common, we've noted a spike in candida or fungal infections, as you see here, in green, versus the traditional full thickness corneal transplantation data in red.

So, disturbed by this, we have done some research and Dr. Elmer Tu showed that fungal contaminates can be amplified in storage media by more than 100 times when routine warming cycles are done as compared to a single warming cycle and from this, we have now put out an RFP for the addition of antifungals to media to try and prevent this moving forward but as discussed previously for industry, this is not a large source of revenue and we have not found any

interest from industry to date about the addition of antifungals to corneal storage media. So in summary, avascular -- the cornea is avascular, disease transmission is rare. Our recipients are not tested prior to receipt of a transplant. We do not screen them for hepatitis B, C, HIV, CJD, etc. we are tracking the adverse reactions both initially and at three to six months and our hope is that modern donor screening has and is evolving greatly and we think it's very important to protect our recipients and protect the public so thank you very much for your attention.

DR. KUEHNERT: Thank you very much, Marian, now we have John Miller from the National Marrow Donor Program talking about infectious disease transmission and stem cells.

DR. MILLER: Great. Thanks, Matt, I appreciate that. I also appreciate Mike Strong and the discussion in the first session that set my talk up on some of the key points I wanted to make on how hematopoietic stem cells are both similar and very different from the other types of

tissues that we are talking today so thanks for that and we'll hopefully share some data.

So really when we think about hematopoietic stem cells, we want to look at what do we think the infectious disease risks are and what are the clinical impacts for the transplant patients who receive the products who are very different patients than the patients who are receiving either tissues or organs or blood products and I will start with a slide just basically what are the type of products we are talking about now but also what are we thinking are going to be the products in the future because when we think about cellular therapy and regenerative medicine, a lot of those therapies are basically using as their initial starting material the types of stem cells that we talk about as the hematopoietic stem cells.

We'll talk about the differences between blood, tissue and organs and how that also can be a positive negative. It's different but on the other hand, we can learn a whole lot in the

hematopoietic stem cell world from the other tissue products that are donated because you have a whole lot more products than we do so that's one of the big differences.

And then we'll talk a little bit about Zika and what we've learned about Zika so when we think about all of the science we are talking about, what are all the practical implications of implementing new strategies for screening for emerging infectious diseases.

So when we think about what types of hematopoietic stem cells we have, the traditional source has been bone marrow collected in the OAR from the posterior iliac crest. Peripheral blood stem cells, basically these are collected from the peripheral blood after we've used a mobilizing agent to get the cells to leave the bone marrow into the blood stream so we can collect them and then the most recent stem cell product for hematopoietic cells, umbilical cord blood.

And one of the key things I think we'll talk about in the discussion section is cord blood

is the difference that it's cryopreserved and banked so that raises some interesting questions and possibilities for research questions.

We have different types of stem cell transplants as to where the donor source is so it can be an autologous self-donated for something like a Hodgkin's or non-Hodgkin's lymphoma. It can be a related -- either a twin or an allogeneic and this is important when we think about the different screenings but also they are regulated in different pathways, right, Melissa? And then what I am involved with day to day, obviously is the unrelated, where we are trying to match a donor from anywhere in the world with a patient anywhere in the world who needs a life-saving transplant.

First of all, how are hematopoietic hematoprogenitor cell donors similar to blood donors? Well basically, they are blood if you think about it. They are regulated differently and they contain different cellular concentrations but they are all basically derivatives of blood.

They all contain the cellular and plasma components of full blood, they are collected from whole blood -- peripheral blood, the -- as I said, cord blood is cryopreserved so that is different and while they are not progenitor in nature, we do use mononuclear cells as a therapeutic modality for tumor recurrence and also for viral specific infections that happen post-transplant and so really when we think about one of the positive things is we can look and say the risk for infectious disease transmission is going to be very very similar to what we would expect in the blood industry and clearly there are a whole lot more blood products collected every year and I'll show you the data for us and there are stem cell products.

Well how are the donors of hematoprogenitor cells different from those whole blood donors. Far fewer, so orders of magnitude different so when we think about the data that was presented by the speakers in this section, they have a lot of data on the number of cases. Well

fortunately, we don't have a lot of data on the number of cases because we don't have a lot. So that's good, so we really do need to look at other tissues to help us predict what might be emerging.

HLA matching is more critical in stem cells than it is even in tissue and so we often have a case where there may be only one donor for a particular patient and so we have a transplant physician who needs to look at the clinical risks of not proceeding to transplant versus what might be a screening risk and we have a pathway that we can have those donors actually donate with a transplant physician's approval. We also have a large number of our products that are not collected in the United States so again the HLA matching, the tissue type matching means we are going to be having the donor maybe someplace else in the world and I'll show you how often that happens and we also have the difference of the gift of time so with our donors, we've got the opportunity to have a longitudinal evaluation over weeks to months of our donors before they donate

and we have that same ability and we do look and follow up with each and every donor after their donation, until they are fully recovered and we also have some long terms studies going on so different timelines as well.

Some other differences, our products are infused fresh so we have them similar to the corneas. They are infused hopefully within 48 hours of collection so if you were to get a positive test result on the day of collection, often the product had already been infused or would be already infused. Pathogen inactivation technology, I am surprised with the blood bankers we haven't mentioned that yet but most of those technologies work on mitigating the replication of DNA, that's exactly what we need our cells to do. They need to go in and they need to multiply to beat the band and engraft so we don't have some of those options to mitigate infections disease that might actually be present.

And then obviously, our patients are (inaudible) or at least reduced

intensity conditioning. They may die if they don't get the product that we have collected and so we have a life and death decision if something happens that precludes that so anything on the last minute is really not good.

So now I am going to get to some of the data slides here. So if we look at the number of transplants that occur in the U.S. each year, you can see the total number of transplants is the height of all of the bars but blue is bone marrow and so that was the first source of hematopoietic progenitor cells and then peripheral blood stem cells or HPC(A), took over and then we have (inaudible) and then you'll notice the interest -- whoops - - well if you look way over on the end, the numbers are flattening out, which is different, and we can talk a little bit about why that may be.

So I talked about HLA being so important

a factor in determining clinical outcomes. This slide looks at the data in a good risk patient, what's the likelihood of survival if you decrease the HLA matching and so if you have an eight of eight, a perfect HLA match, 50 percent survival. If you now have a seven of eight, it drops to 39, six of eight, it drops to 28 so you are dropping or 11 percent every time you go down in a match grade. That's like should you take the liver with hepatitis C? The patient dies so you don't want to have a risk that's infectious disease that's small in magnitude compared to this, that's a clinical decision that has to be made. So this is a good news bad news slide but it shows you the likelihood of finding a donor so what's the likelihood that if anyone in this room were searching based on your ethnic background, what is the likelihood that you'd find a match?

The good news is the total height of the bars which looks at the different sources and match grades put together, it's all over 90 percent, that's great. Throw in haploidentical

donors, basically the message of not everybody had a donor has switched to almost everybody does have a donor which is a great message but you can see it varies by the ethnic background but the bars add up with the blue -- the light blue on the bottom is if you have an eight of eight.

So we said we want everybody to have an eight of eight, it has the best outcome, right? If you have the seven of eights, that's the light green, it jumps up a whole lot but we know about impact survival and then if you add the different cord blood match grades, that's how we get up that high but again, HLA is a key part to what we do.

We talked a little bit about international exchange. It's really an amazing thing when you look at our world, our culture, everything that's going on, we get to work in a field where the world really cooperates and so if we look internationally, the data from the world marrow donor association and you look at the number of transplants where the donor and the recipient were in different countries, that's the

international in red or they are in the same country, well lo and behold, the numbers actually overlap so you can't read them. Half the time, the donor and the patient are in different countries so it's truly an international endeavor but that also raises the questions from an infectious disease perspective, we truly do have like that slide in the first session of the diaspora of our products are going all over the place, all over the time.

For our patients, 40 percent of adult donor products come in from other countries so it's true to us. It's not just countries around the world, this is a phenomenon that's pretty general.

I talked a little bit about we have more time to do an evaluation of our donors and it can be very thorough and it is, and having a small number of donors, we have the resources to do that. So as we think about going through the evaluation of a donor, when they first come up as a possible match and we do our confirmatory

typing, we will do infectious disease testing but we are not going to do any medical evaluation history and physical exam but as you go through, you are doing a more complete medical evaluation so that we are getting a complete medical history, obviously a risk history, physical exam and then another key part is after donation, we follow them to make sure they are clinically recovered but we are also looking to say do they have any infectious disease or any symptoms of it so we've got a wonderful cooperation with our research arm that works with all of our hospitals to gather all of this data so we have an automated and efficient process to do that.

I basically said that in the last slide. So a couple of slides and then I'll be done. Infectious disease transmission in hematopoietic cells transplants are very very rare so basically we can transmit anything that you would think historically we could transmit, right? Bacterial transmission, not uncommon in marrow that the product comes up with a positive culture.

Again how often do we see an actual clinical event? It's really rare. We had a possible salmonella so that raises the issue of a different organ system with a reservoir that could be making something appear in the bloodstream at the time of collection and viruses like hepatitis B and parasites like malaria so we have live cellular products or even frozen ones that have been cryopreserved with the intent of making the cells viable in what we do so basically proof of principal, we can transmit all of those.

We talked a little bit about related donors. There is more infectious disease transmission historically in related donors but that's because they were the first source of donors before the unrelateds so they were in the prescreening for a lot of things like HIV and the transplanters historically have used patients who are hepatitis B or C marker positive for their transplants and lo and behold, you see things so -- and then one that I am surprised Ted did not put in his talk because he loves this case is the

transmission of the HBV setting because the contamination of the liquid nitrogen storage tank so I thought that would be --

Last slide here, Zika. So we had fun over the last year working with Zika and putting into place the recommendations for screening and the interesting things are that the geographic spread continues to change, the reports lag behind when the infections occurred. Like I said, our donors are assessed weeks to months. They may travel in the interim and you have to make sure you are able to get that history. The real interesting one is the partners. You have know that male sexual partners, where they have traveled in the last six months and when we first had that, you are telling me this when it's spring break season? But it's actually worked out, we've done well at doing that so really when we think about the way we put in screening for donors historically, you didn't have a lot of change. HIV was a risk, it was a risk. We kind of knew what the risk factors were. Zika has been a case

where every time you get something in place, something along the line changes of a different geography or now we learn that sexual partners actually can be a risk factor so we've basically looked at our processes and said for some of these new things, you can't change all your hardwired infections -- IT and all that sort of stuff, you need to have a very flexible and (inaudible) to be able to implement those and so we actually -- we have gone with the supplemental questionnaire with the questions so we can change those without having to go to IT and go -- okay, 18 months and the next cycle for that software development, right? So I think -- so then that basically summarizes what I've said, the differences between blood donors, tissue donors but the one point that I emphasized to keep myself on time here is for emerging infectious diseases, we have to remember the emerging cellular therapies, think about all the different cellular therapies in regenerative medicine that's coming along, our car t cells, cytotoxic t lymphocytes and all these things.

What are the infectious disease risks that we are going to be looking at in those tissues either before or after they go through all the manipulation and genetic engineering to get them to be what they are going to be.

So I think that's going to be probably the most interesting area when we look forward in hematopoietic cells is with all the great promise of cellular therapies, we have to be thoughtful about that as well so I think I will stop there.

DR. KUEHNERT: Okay. Next we have Dr. Deborah Anderson talking about infectious disease transmission by reproductive cells and tissues and we're just a little behind so I think what we are going to do is we are going to see if there are any questions for speakers until after lunch when we'll also have the panel discussion.

DR. ANDERSON: Thanks, Matt. I'll just quickly cover the history of assisted reproductive technology and how infections have impacted the field and how we've adapted to the infections with our guidelines and practice.

So the field really got started with sperm insemination by donor and that was a thriving industry in the 70s. Several sperm banks were formed then and surveillance in the infectious diseases in the sperm banks at that time was pretty informal. They screen their donors for the known serious treatable STDs, syphilis, chlamydia and GC but other than that, there wasn't a formalized screening program.

IVF was first described in 1978 and by the early 80s, there were several IVF centers in the U.S. and of course, this is about the time that HIV appeared on the scene so we'll be talking about that in a minute. '83, there was the first pregnancy with donor eggs, '84, the first surrogacy embryo transplant and then we got ovarian tissue transplants and probably beyond in the next few years with testicular transplants.

So the AIDS epidemic happened pretty much concurrently with the IVF program growing and it of course affected the field because there were several early transmission in the sperm banks.

There were three reports in the 80s of transmissions that had occurred early in the epidemic before screening for HIV. In New York, 176 women were inseminated with semen from six HIV infected donors and one seroconverted.

On the west coast, 230 women were inseminated with semen from six HIV infected donors and seven seroconverted. There was a ninth case -- an eighth case reported by the CDC in 1990 where a woman was inseminated with sperm from her husband who was a known HIV positive man. The sperm had undergone a washing procedure but she was infected nevertheless so there are eight bona fide transmissions and the CDC says that there are maybe may more that occurred that just weren't followed up. So the way our field dealt with HIV transmissions kind of mirrors the stages in dealing with new pathogens in general.

The first step was to identify and exclude the high risk groups and in this case it was the gay population and IV drug users and then as soon as screening tests became available, they

were applied and first there is serology which isn't as specific as it can be and then later there are nucleic acid tests which are much more specific and reliable and finally, as the epidemic matures, you've got risk reduction measures that can be taken such as treatment and vaccination and in the case of assisted reproductive technologies, we've got sperm wash which is used quite extensively in some clinics. So this is the evolution of the HIV guidelines in the ART field. The CDC reported in 1985 that semen donors should be excluded from the high risk groups and then in 1990, they advised sero testing for all semen donors and this even included direct semen donors within intimate couples and that's because of that one case where they found that there had been transmission even with a sperm wash protocol.

So for a long time, the U.S. has complied with the recommendation that there should be no inseminations with semen from HIV -- sero positive men and this means that all ART clinics test their semen donors, even if their husbands

indirect inseminations.

And finally, the FDA recommended in 2005 that all semen, oocyte and embryos be regulated as HCT/Ps under their published guidelines so the field evolved with the evaluation of the FDA guidelines in this area.

Now this is a specific case to the ART industry and it started with the Brandon versus Abbott Supreme Court Case which ruled that HIV positive individuals are protected from discrimination under the Americans with Disabilities Act. This means that HIV infected individuals are entitled to assisted reproductive services and the society for reproductive medicine, the ethics committee which I served for many years really struggled with this case because the CDC on one hand was saying that we couldn't treat HIV positive sero discordant couples yet we have this Supreme Court Case saying they should be entitled to our services.

The Europeans were ahead of the curve in this regard. They started offering sperm wash

procedures to lower the risk of HIV transmission from seropositive male partners and this started in the late 80s, a clinic in Milan and most of the blood borne or systemic viruses will appear in semen and seminal plasma and in the case of HIV, it appears in semen on a fairly high concentration in the white blood cell fraction.

There are a number of white blood cells in semen, variable numbers but careful studies show that there was no HIV associated with the sperm themselves so the -- the viable sperm. So the Europeans developed this two-step sperm wash procedure which they still widely use for HIV and for some other systemic viruses that appear in semen. They first process the semen through a (inaudible) which separates motile sperm from other fractions in the semen, the infected white cells for example, will segregate here and the seminal plasma stays above so they've got washed sperm here that separated from the white cell

fraction and then they do a second separation -- they swim the live sperm up from the pellet and collect the sperm at the top of this column so they've done a two-step wash procedure to separate the motile sperm from the HIV contaminated fractions and they continue to do this but this was their first report in 2007, eight European centers at the time were offering sperm wash for HIV positive men with HIV negative partners and they reported 3,396 treatment cycles and no seroconversions.

And these numbers have about doubled and there are still no reported seroconversions with the sperm wash procedure. In the U.S. the industry has been more hesitant to do sperm wash because of the possibility of litigation. Mark Sauer at Columbia has been treating a lot of

discordant couples here with ICSI and he reasons that he is not inseminating the women with the infected sperm, he is inseminating the oocyte and then putting the embryo back in.

So he performs ICSI with sperm from infected men and has done over 400 consecutive cycles and has not had any seroconversions. So this has been the way that our ART industry has dealt with the HIV epidemic. HIV has raised our awareness of other systemic viruses that can appear in semen, like HBV. It's even more infectious than HIV. Luckily we have a vaccine so, with the luxury of time, we can vaccinate the recipient before inseminating with HBV positive semen.

There is no indication for sperm washing since you can immunize the uninfected partners. HCV is also potentially sexually transmitted but the risk is low. They screen semen donors for both HIV RNA and for HCV serology but it's the RNA positive men that you have to be worried about and they may benefit from sperm washing since the few

studies that have been done in this area have shown that the HCV virus is not associated with sperm.

HTLV 1 and 2 are retroviruses that appear at low prevalence in the U.S. and at higher prevalence in Japan and some other countries. It has the same infection profile as HIV. It primarily affects T Cells and we know that T Cells can appear in semen so sperm wash would probably be advisable in these patients if you had to make a choice. So moving forward into the emerging epidemics that are sexually transmitted, there is the threat of untreatable GC, our old STD friend so we might see untreatable GC cases in our ART clinics so we need to be vigilant in that regard. There is molecular evidence of the sexual transmission of Ebola virus and it appears that some of these systemic viruses actually persist in the genital tract after they are cleared from the blood. Ebola is one such virus and, of course, Zika is another -- we've recently found that Zika is present in semen, it's sexually transmitted and

it can persist in semen long after it's cleared from blood and here is one example from a case that was worked up in Toulouse, France. A man traveling from French Guyana with a Zika infection and they found high levels of the Zika DNA in semen long after it cleared from plasma and urine so it seems to hang out in the genital tract maybe because the genital tract has some immunological barriers. The testis is considered a privileged site and they took a picture of an HIV infected -- of a Zika infected sperm. They used an antibody shown with a fluorescent marker here against the Zika protein and speculate that the spermatozoa themselves may be carrying Zika virus.

This is a very early report. It hasn't been confirmed but this might be a case where you can't wash the sperm, that the sperm themselves might actually be carrying the virus, well worth keeping an eye on. So let's see -- so our guidelines for Zika in the ART clinics are at the earliest stage of development where of course, we are getting travel history from all of our ART

donors and we don't allow insemination if the traveler has been to a Zika endemic region in the last six months and we are starting to use the Zika serology and map test to identify these potentially infectious people.

So in conclusion, there are a lot of sexually transmitted pathogens, some of them are the classic pathogens that infect the genital tissues like GC and chlamydia and trich and syphilis. Others are systemic pathogens that make their way into the genital secretions and are also sexually transmissible. So far, the risk of transmission through reproductive cells and tissues has been low, in part due to vigilance and rapid implementation of guidelines for identification of risk groups, testing and treatment. Thank you.

DR. KUEHNERT: Okay, for our final talk before lunch, Dr. Brandy Clark from the FDA talking about relevant communicable disease agents and diseases.

DR. CLARK: Okay, today I am going to

talk about relevant communicable disease agents. I'll go over a brief overview of donor eligibility requirements and then I'll give an overview of the RCDADs. I'll define and list the current RCDADs, then I'll go over how FDA determines whether a communicable disease is an RCDAD or not based on the regulatory requirements and we'll give a couple of specific examples such as West Nile virus, Ebola virus and Zika virus.

So briefly, donor eligibility requirements or donor eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases is required for all donors of human cells and tissues and tissue products.

HCT/Ps must also not be implanted, transplanted, infused or transferred until the donor has been determined to be eligible except as provided in these regulations here. So relevant communicable diseases and disease agents or RDCADs is defined in 1271.3(r). There are two groups of RCDADs. The first group defines the current list

of RCDADS -- or the specific relevant and communicable disease agents when the regulation was first published. The second group is basically how we go forward when there is an emerging infectious disease and we determine whether or not it's an RCDAD or not.

So defining additional RCDADs, if the FDA determines that an additional infectious disease meets the criteria for an RCDAD under the 1271.3(r)(2) regulation or conversely if it determines that an RCDAD is no longer -- meets the criteria, then it can remove it from the list and the agency will notify the public via a guidance.

So the general criteria that is listed in 1271.3(r)(2), you can see it here on the screen. It can be divided into three groups basically so the risk of transmission by HCT/Ps to the recipient or to those who handle the HCT/Ps or come into contact with it, then there's the risk to the HCT/P donor population and this gets into the incidence and the prevalence of the disease, then there is a risk to the population which is

the severity of the disease, is it fatal, life threatening, does it cause permanent damage to the body et cetera, and then lastly, we look at whether or not there are appropriate screening measures and testing that's in place.

So here you can see -- so you can hear me? -- Here you can see a slide that lists the current RCDAD screening and testing we have in place. Let me go back and see if this -- there we go. So we have Zika on here and then we have West Nile which are two emerging infectious diseases that we've dealt with in the last decade or so and then we've recently published a guidance on West Nile virus NAT testing and living donors, which was published in September of 2016.

So additional RCDADs that meet that criteria under 1271.3(r)(2) -- I'll go over the three that I mentioned earlier. We focused on West Nile virus but as you can see by the slide, when the final rule was published in 2004 and then following that there was a DE guidance that was published in 2007, there was an ongoing epidemic

of West Nile virus and that was eventually an emerging infectious disease and we'll go into why it met the criteria for an RCDAD and it was listed in the DE guidance that was published in 2007 as an RCDAD to be screened for. So West Nile virus, risk of transmission -- so there is evidence of transmission via organ transplantation and via blood, components, stem cells.

The pattern of transmission is geographical. The spread suggests that most or all the U.S. is at risk and activity of birds and mosquitos, it's year round in the warmer climate so the risk to humans is year round so your risk to the donor population is significant. So then we look at severity of effect and, as you all know, West Nile virus is responsible for encephalitis and meningitis epidemics. In 2002 it was responsible for the largest meningitis encephalitis outbreak to current North America. It's caused fatalities, it causes permanent and neurologic such as Guillain-Barre syndrome.

And the other thing that we look for, as

I mentioned previously, is are there appropriate screening measures and testing in place? So when the West Nile outbreak was going on, screening measures were developed. You can screen by medical history, you can do a physical exam and assessment to see if a potential donor had West Nile virus or had been possibly exposed to West Nile virus and then eventually a licensed nucleic acid test came along and then we published draft guidance and eventually a final guidance in the use of nucleic acid testing.

So challenges going forward, emerging and infectious diseases, to be or not to be an RCDAD, that's the question. We are going to go over a couple of decisions that the FDA has made and why they made them in the last couple of years. We'll focus on Ebola virus and Zika virus and it gives you an idea of why they are or not an RCDAD. So Ebola virus disease, the risk of transmission -- there have been no documented cases of HCT/Ps but as someone mentioned earlier, it can be found in the secretion of the eye,

aqueous humor, it can be found in semen for prolonged periods of time so there is the potential risk for transmission.

There are uncertain periods of time of asymptomatic viremia and there is risk of transmission through contact with body fluids, that's well known. It's in the blood, it's in urine, stool, saliva, semen, vaginal fluids, vomitus, et cetera. But the overall incidence or prevalence of the U.S. population, particularly of human cells, tissue, and tissue products is relatively low.

Severity of effect, we all know that Ebola virus is a hemorrhagic fever virus with high morbidity and mortality. Mortality rates are upwards of 90 percent in some outbreaks. A 2014 outbreak that occurred in West Africa, you can see here some statistics, they were upwards of 28,000 suspected or probably or confirmed cases and almost 11,000 deaths reported as of April 2016.

And between 2013 and 2016, in the U.S. we had 11 cases of Ebola virus disease, nine of

which were acquired outside the country and only two deaths. So are there screening measures or tests that we can do for Ebola virus? Well there are screening measures of course. You can do a medical history, you can do a travel history, you can do a physical exam but there is no licensed or approved tests for donor screening. So based on that, Ebola virus disease did not meet the criteria to be a relevant communicable disease based on what's in the regulations of 1271.3(r)(2). It didn't have sufficient incidence or prevalence to affect the population of the United States and the other criteria that I didn't mention previously but it's also in 1271.3(r)(2), is that the Ebola virus disease, as you may or may not know, can be a bioterrorism agent and one of the criteria that's in 1271.3(r)(2) kind of deals with this, is that it was not released accidentally or intentionally in a manner that places your donor population at risk so therefore it could not be defined as an RCDAD.

Now on to Zika virus. In January 2016,

Zika virus became a nationally notifiable disease in the United States and then in February 2016, the World Health Organization declared a public health emergency of international concern. This was based on clusters of microcephaly and other neurologic disorders such as Guillain-Barre syndrome and their possible association with Zika virus.

By then, there was transmission of Zika virus in 28 countries and it was rapidly spreading out from South America through the central Americas and the Caribbean with the anticipation of it hitting the U.S. mainland very shortly thereafter.

So risk of transmission. There has been evidence of transmission of Zika virus via blood transfusion. Some studies show that there was three percent of asymptomatic French- Polynesian blood donors that were positive for Zika virus, RNA by NAT testing during a recent outbreak. In 2016, nearly one percent of blood collected from asymptomatic donors in Puerto Rico were tested

positive for Zika virus and there have also been case reports for Zika transmission via blood and platelet transfusions in Brazil.

You can get it from the bite of a mosquito. There is maternal fetal transmission. Other people have already gone over the sexual transmission of Zika virus but vaginal, anal, oral sex, male to male transmission, female to male transmission, et cetera. There has also been a case report of laboratory exposure here in the United States so there is a theoretical risk of transmission of Zika virus by HCT/Ps. Yet, as you can see here, there is a brief summary of those stats in the United States as of late January, courtesy of the CDC. We have 219 cases of local mosquito borne Zika virus in Florida and in Texas, most of that is in Florida.

Okay, so severity of effect, this is not all inclusive obviously but there is fetal loss that can occur with Zika. It causes congenital microcephaly, Guillain-Barre syndrome, encephalomyelitis and transverse myelitis which

can be devastating and cause a lot of disability, meningocephalitis. There are a lot of ocular effects that have been associated with Zika virus in the pediatric population and infants, cataracts, retinal dysplasia and retinal atrophy have been reported and then adults, uveitis has been reported as well.

So in March of 2016, we published guidelines for industry on donor screening recommendations to reduce the transmission of the Zika virus in the HCT/P population and so this met the criteria of availability of appropriate screening measures. This was based on the available evidence, scientific evidence that was available to us at that point and time, so screening measures were available. You could screen with a medical history, travel history, deferral, and physical exam but at that point and time, there were no licensed approved tests available for donor screening.

So based on all that, we met the criteria for an RCDAD under the regulation. There

was sufficient incidence prevalence to affect our patient population or donor population. There was severity of effect and then screening measures could be implemented. So in summary, we went over the definition of relevant communicable disease and disease agents or RCDADs. We listed what the current RCDADs are and then we went over the regulatory approach the FDA takes to designating how emerging infectious disease can become an RCDAD or define an RCDAD or not and the key regulation for that is 1271.3(r)(2) and the key take home points are for an RCDAD, for an emergent infectious disease is a risk -- what is its risk of transmission, what is the severity of effect and are there are available screening and testing measures and that's all I had. Now we have lunch.

DR. MCCLURE: All right, just a couple of little quick information about lunch before we break (sic). We're running a little bit late so we are going to meet back here at 1:50 to have the panel discussion for this session. Unfortunately, I think we will have to cut it a little bit short

but we'll meet back here at 1:50. Lunch is available for purchase in the café that you passed when you entered the building. To get to the café, you have to walk back out the front entrance of the building that you came into and it will be through the glass doors immediately on your left.

It may take a little while to get this many people through the cafeteria so I do want to ask if you see our speakers from this session out there, maybe push them to the front of the line so they can make sure they can be back here and ready for the panel discussion. As far as places to eat, to sit and eat your food, there are some tables outside if you want to walk around the building, it's actually nice out right now. You can walk around the building and there are some tables kind of basically behind us. There are some tables in the café and there are some tables that have been set up just outside this room. In addition, I know the signs say no food in this auditorium, however, because our original plans that they said they were going to make for us fell

through, they've made an exception so you can eat here if you'd like, just please be sure to clean up after yourselves.

And then one last thing for our speakers, we do have an extra room reserved if you guys want to join us in there. It's 1b42. It's in an area that is FDA access only so we will try to have some FDA folks standing by to escort you back if you want to join us there for lunch. The door is by the main doors, left to the door by security. All right, thank you. We'll reconvene at 1:50.

(Recess)

DR. KUEHNERT: Okay. We have our panel made up of previous speakers here. Who are we missing? We're missing John and Brandy.

Okay. So, while we're waiting for John and Brandy, does anyone have any questions for the speakers who are here? We know we skipped the Q&A before, so I just wanted to make sure that if you have any burning questions on presentations, that you have an opportunity for that.

Okay. Hearing none, we'll move to the discussion panel. The first question is: Does knowledge of various modes of infectious disease transmission, such as sexual transmission or laboratory exposure, extrapolate to risk of transmission by HCT/Ps? And how can we extrapolate from observations of other human-derived products, such as blood and/or organs?

So, who wants to start, on the panel, on that one? Dr. Eastlund.

DR. EASTLUND: Can you repeat the questions?

DR. KUEHNERT: Sure. Let's start with the first part of it. Does knowledge of various modes of infectious disease transmission, such as sexual transmission, lab exposure, etc., extrapolate to risk of transmission by HCT/Ps?

DR. EASTLUND: You can obviously hear me. Well, of course, using the knowledge of how a tissue transmitted an infection and learning what went wrong, tells you what you can do in the

future. Is that sort of the question you're asking?

DR. KUEHNERT: I think the question is, if you see transmission in any way of a pathogen, how does that extrapolate to risks of transmission by HCT/Ps?

DR. EASTLUND: Okay, well then, as you have a table there showing that many diseases have been transmitted through bone marrow, through blood, through organs, that arouses you to worry about that for tissues. And so, it informs, that we're going to get it ourselves also with tissues eventually if you're not careful.

DR. MACSAI: Well, I think it makes us investigate a little bit more about more details, about the mode of transmission. And it's very important because we could exclude a huge amount of donor population. So, there's always this risk-benefit ratio that we have to be looking at.

And that's why I think the devil's always in the details. And we're riding that very tight rope between public perception of risk and

true risk, which is very different.

DR. ANDERSON: I'll use an example: The sexual transmission of HIV, that's the virus we have most experience with. Not only is the amount of virus in the semen, when it's transmitted through semen, a factor and viral load is a factor, but there's also susceptibility in the partner. And there are a lot of people that think that HIV's not transmitted unless there is susceptibility in the partner. And inflammation is one of the susceptibility factors. Maybe the woman also has an STI, which makes her more susceptible. So, in that case, it's not directly applicable to the tissue transplantation model.

DR. KUEHNERT: Dr. Clark, any comment?

DR. CLARK: The answer is yes and no. Because you can have a virus in a tissue, but it may not be live virus, and it may not, you know, infect the person.

So, I think you need studies to evaluate and then determine what, you know, what the transmission is for your HCT/P population. And

you can't necessarily extrapolate from the general population. You need to study your donor population, if that makes sense.

DR. FISHMAN: Now, can I just make a comment in that regard?

DR. KUEHNERT: Yeah.

DR. FISHMAN: The question may relate -- it's Jay Fishman -- more to the assays we use, which is really the subject of the next section.

But if you're measuring the wrong compartment, blood or serum for example, and it turns out to be a tissue-derived pathogen, then it's hard to figure out. And that's where we get in trouble. And then, of course, there's window periods and latency and the like.

I would use, perhaps, a couple of examples: One was the rabies that was derived from the artery conduit that was used. And we already knew that there were at least four recipients of organs that had contracted rabies from the same donor. And yet, none of us really thought you could get rabies from an artery. And

so, all five were informative in terms of neurologic disease transmission.

And I think the other was, perhaps, the early experience back when Hepatitis C was non-A non-B. And even when we were transplanting livers, it wasn't 100 percent transmission. So, at least it showed us there was a lot we didn't know about the biology.

And I think the third point I would make, is that this should focus our research in terms of thinking about where we put research dollars in this field, in terms of thinking about the biology and how to extrapolate, to not just blood and organs, but also, to other tissues that are -- particularly, those that are not processed.

DR. MACSAI: I want to piggyback on Dr. Eastlund's comment. Because while in organs, as we said, we're testing the recipients in blood, most tissues, corneas, reproductive, we are not testing the recipients. And so, we have to be careful about our definition of transmission. Because if the recipient is in the window period

of infection, it may appear to be transmission when it's not. So, it does become quite complicated.

DR. KUEHNERT: Could you restate that? I didn't quite follow that.

DR. MACSAI: If the recipient is infected before they receive transfusion, whether because they're already super sick or immunocompromised or whatever, then they may appear to have had the disease transmitted through the transplant, be it blood, tissue, whatever. But in fact, it's either reactivation of their own disease or they were already infected prior to the transplant. Or in some patients, we may have false data because they're so sick when they're getting the transplant, they pass before we even know if disease was transmitted.

DR. KUEHNERT: Right. So, that's the point you made earlier, which is a very good one, that if recipients are not tested beforehand, then you don't know whether they got infected due to the procedure or were already infected.

The other thing is that, you know, some data was presented, but there's more out there. I think what is most telling is those investigations in which there was a known positive donor, there were known organ and tissue recipients, and the tissue recipients that were negative. Those are the ones that really tell us a lot about that transmissibility, perhaps, as potential but did not happen there. And for instance, corneas. You know, there's a lot that, you know, we can learn from what's already been done.

The other opportunity out there, and I can't tell you how often this happens when we do investigations at CDC, is when we find a recipient is positive, there's a donor serum that shows evidence, say through antibody, that the donor was infected. But there was no autopsy.

Such an opportunity lost. And I don't know how many pathologists there are here in the audience, but that is really something that I feel like we all could work together on, is to improve the percentage of people who get autopsies that

become organ and tissue donors.

Okay. So, are we ready for the next question? Number two. Oh, I guess I'm supposed to do that. Oh, good. Okay.

What is the applicability of animal models for the purpose of predicting potential transmission in humans by HCT/Ps?

DR. EASTLUND: There are some obvious times when it's applicable. If you're studying whether syphilis can be transmitted, you can't really culture it. You use animal models to see if it's still there or if the infections there.

So, that would be an example of needing an animal model just to document that something is infected or transmissible or transmitted.

I don't know all the other diseases and all the other tissues, but I think these can, well, I guess we have the guinea pig assays and stuff, too. But I'm sure that animal models can inform us for many aspects of disease transmission. So, I think there is plenty of room for maintaining research and studies on those

models.

DR. ANDERSON: The macaques model within the HIV field has been very valuable. It got the simian HIV virus, that transmits in much the same way, that HIV transmits. And they use this model to study interventions and mechanisms.

The other model that's used in the STI field is the mouse model. They've got the humanized mouse model for HIV transmission. I'm not a big fan of it. It has human T cells, but it doesn't have a human epithelium, human dendritic cells. There are a lot of problems with it.

And then, with the Zika transmission, there have been a few studies in mouse models. But they knock out the interferon pathway to get infection, and I just wonder how physiologic that is. We need to keep developing models.

DR. KUEHNERT: Any comment from the audience on this question?

DR. MILLER: Yes, I'll just make a comment. When we think about the mouse models, which obviously, in transplant, are very, very

common. And it gets at the whole thing of the immunocompromised, whether it's the animal or the patient to mount an immune response to generate what you're trying to detect. And so, a lot of the antibody based models and whatever, you might actually, you know, miss, you know, infections that are in the models that we use in the transplant world.

DR. KUEHNERT: That's a good point. So, for animal models, we have to take into account, immunosuppression, perhaps, of a knockout model that fits the population.

DR. MCFARLAND: So, Richard McFarland, FDA. And I was once upon a time a pathologist, so I got your point about missing autopsies. They're not very interesting once organs and tissues have been recovered. So, there has to be a way to incentivizes hospitals to do that. I'll see, I'll talk to some friends that are still doing it.

But to the point on animal models, the importance of animal models: One, is understanding the disease, understanding the

kinetics of the disease, and tropism of the disease.

So, I think it might also be worthwhile, thinking beyond traditional animal models, but think about, particularly, zoonotic diseases that have the actual host in veterinary systems and study those models. Particularly, in the HCT/P world, when you're worried about where is this organism? You know, which tissues is it in? How long does it stay there? That kind of thing I think could be really helpful. But otherwise, to some degree, we're flying a little blind until we get human data on that.

DR. KUEHNERT: Okay. Other comments from the audience or the panel on question two?

Okay. We'll move on to number three. Oh, sorry.

DR. KIBALO: Excuse me. My name's Ben Kibalo, I'm from DSM Biomedical. I'm a medical device guy, so this may be a segue to question three.

Looking at the sterilization methods

that have been adopted, I feel like with the HCT/Ps, since it's not a medical device, for those ones that are being sterilized, there's an opportunity to dial back some of that overkill sterilization methodology. Is there any desire or science behind, you know, doing a gentler sterilization versus a half-cycle overkill method, 20-log reduction type that you would do for a normal med device, that maybe will improve the performance of some of these tissues when they're implanted?

DR. EASTLUND: Can you rephrase the question? Any desire for --

DR. KUEHNERT: Yeah, could you please?

DR. KIBALO: So, I'm really just wondering if -- I guess to phrase it another way, how was the sterilization methodology adopted? Was it taken more from the medical advice side of things where you have a sterility assurance level of 10-6, which is pretty extreme from a biologic performance standpoint. You know, you're not going to have a million bacteria on your device

that you have to kill. It might be like a 100 to the power of 10.

So, could we dial back the sterilization methodology to make a more biomimetic and more biologically available scaffold instead of just scorched earth, killing the whole thing for the sake of safety? Does that make more sense?

DR. KUEHNERT: Yeah.

DR. KIBALO: More sense?

DR. KUEHNERT: Well, I think we need to call an FDA friend to help us out with this somewhere, to explain, you know, the variability in processing methods in tissue. Because I think that's important to your question.

DR. MCFARLAND: Okay. So, the answer to that question I think, is product specific. When we're talking in this meeting of HCT/Ps, we're talking about HCT/Ps, which are regulated under the tissue rules, so-called 361 HCT/Ps and the so-called 351 HCT/Ps. Those have different standards in order to market them and different manufacturing interactions with the Agency in

terms of review and whatnot.

And the level of most tissues, aren't labeled as sterile, even if they've had pathogen-reduction technologies or X-rays done on it. So, how much sterilization and pathogen-reduction manufacturing is done on tissues is really a largely manufacturer-specific question. And there are some for which they are similar to the traditional medical devices and some of which that they aren't.

DR. KUEHNERT: Question up there?

DR. SCHULTZ: Dan Schultz from Tampa. Ted's data kind of showed it. I mean the grafts that were out there were non -- the one's that were processed routinely, those included both irradiated and purely aseptic grafts. And in that population of grafts, it was zero.

I mean, effectively, those -- if you look at the scope of all of the pathogens, we're looking at the envelope viruses and things like HCV. Those were not -- even if you take purely aseptic processed grafts without irradiation,

those -- I'm not talking about the fresh grafts, but the traditionally processed grafts.

My bank for example, for most of my career was exclusively aseptic. No irradiation. It changed when 2010 happened, and we had the group-A strep and clostridial cases that you will discard. So, we started irradiating some grafts.

But the fact is, even with regulated aseptic processing, we have excellent outcomes over decades, without any reports.

DR. KUEHNERT: So, this does segue into the next question, which is how do standard preservation methods; fresh, frozen, cryopreserved, lyophilized, affect transmission? And can we get scientific studies performed that will help the HCT/P field better understand the contribution of different preservation methods?

Now, I'm reading into this, that this is talking about preservation rather than processing. So, what does the panel think of the preservation issue in terms of its impact on transmission?

DR. MILLER: So, in the hematopoietic

stem cell world, we cryopreserve with the intent of keeping the cells alive, right? And we know that in the cord blood world, where we cryopreserve and we bank all of those units, even within the human cells, some survive cryopreservation better than others. The good news is the cells we want do. Granulocytes die, red cells lyse.

So, I think we have to be really careful when we think about the different, you know, cellular organisms that might be emerging infectious diseases. To (inaudible) say ooh, some are going to survive, some aren't. I think from the cells that we do try to cryopreserve, we already know that it varies.

So, my guess is, if we were to look at mother nature, a whole lot of those critters are going to survive, and we already know about viruses. So, I think when we look at the cryopreserved, we're bringing along everything probably.

DR. MACSAI: Our tissue is fresh. So,

not a whole lot of preservation, except that in the preservation media, there's currently antibiotics and not antifungals, which we're currently seeking a way to introduce and work with the regulatory bodies regarding the safety and efficacy. Because in Europe, antifungals are routinely added to preservation media for corneas. So, we are sort of a different animal. We don't have any lyophilized -- I can't speak to that.

DR. KUEHNERT: So, Dr. Strong.

DR. STRONG: I think if you change the order up there and put cryopreserved second, you pretty much have the order of safety. So, fresh is least safe. Frozen, slightly better, although we know lots of things that get transmitted from frozen. Cryopreserved, of course, is cryopreserved. I mean we're cryopreserving everything, if it's done properly, which isn't always the case. And lyophilized, which is processed over and over again.

So, the more processing you do, the lower your bioburden is going to be. And freeze

drying, certainly, goes through multiple steps of processing before it gets to the final stage. So, I mean I think we know quite a bit about how processing affects transmission.

DR. MILLER: The only caveat I would add to that, Mike, because I agree with you in your order and exactly what you said. In our stem cell world, the more processing you do, the more you're increasing the risk of contamination during the processing, with bacteria.

DR. MACSAI: But this is preservation, correct? We're being asked about preservation.

DR. STRONG: Yeah, I think that what I was commenting on is the innate presence of microorganisms that might be transmitted. Certainly, the more you handle, the more chances are you're going to contaminate from external sources, unless you're working in a highly controlled environment.

DR. EASTLUND: So, I answered something?

DR. KUEHNERT: Yeah, I think so. I mean it sounds like the consensus from the panel and

the audience is, as far as standard methods, probably not much.

Actually, I would like to ask, and Ted, if you know the answer to this, how often has a disease transmission occurred despite these methods? Or how often has there been lack of transmission, you know, with these methods from just what we know?

DR. EASTLUND: Well, with preservation in general and the temperatures, the only microorganism, we forget about maybe multicellular organisms in general, but the most famous pathogen is syphilis. That is 48 hours in the refrigerator, and it's dead, period or 72.

So, even just cooling it in the refrigerator kills it. And so, certainly, freezing would also. And I would imagine freeze drying, but I don't know data on that.

But I had the advantage of knowing this question ahead of time, and I was going to have time to show a slide. I gave a brief talk to the Society of Cryobiology in the early 90s on the

effect of cold. So, it made me rethink that, plus look at a few things.

And I'll first mention about fresh things. Things stored at room temperature. Does that mean it's impossible to transmit something? And, of course, it isn't. But we have all these examples of fresh nerve, platelet transfusion at room temperature, transmitted bacteria, mycobacterium chelonae from prosthetic heart valves stored at room temperature, transmitted to many patients, platelet transfusions. We've got intracerebral electrodes stored at room temperature that have transmitted prion CJD from one patient to another. So, room temperature, of course, doesn't do much but allows it.

Refrigerated, there's one example after another of how refrigeration doesn't stop transmission of viruses through skin, cornea, artery, veins, organs, and red cell transfusions. Of bacteria from heart valves, cartilage, skin, and red cell transfusion. Refrigeration doesn't stop transmission of fungus from corneas. And it

didn't stop transmission of CJD through red cell transfusions, three or four cases, and corneas.

But freezing, the same thing. One after another, frozen products of human origin have transmitted viruses, bacteria, and fungi.

But then the question comes up, how about storing as freeze dried? That should be finally the thing that saves us. Of course, that's the way you save bacteria and fungi to sell it from ATCC to people who want viable fungi and bacteria.

So, freeze drying alone does not do that. Freeze drying of the dura and the growth hormone didn't stop prions. Freeze drying of anthrax powder didn't stop its use for biological warfare. And freeze drying of factor VIII for hemophiliacs didn't stop HCV and HIV transmission.

So, none of these actually are a useful step to stop transmitting of diseases from any human substance.

DR. KUEHNERT: Excellent. Yes, sir?

MR. BURKE: Very interesting discussion.

Corey Burke with Cryos International. Kind of illustrates that all our tissues are different. The one that the cryopreservation probably helps with preventing spread of anything, is semen donation, because we have the six-month quarantine. Donors are tested before it goes into quarantine. When it goes officially into quarantine and then after the six-month period. So, there is an example that cryopreservation can help in that regard.

DR. KUEHNERT: Well, that's true. I mean that's kind of an angle I hadn't thought of, which is that if you have a living donor and you can test them multiple times and you have a tissue that you can store in the meantime, then that can help you. But the freezing itself doesn't necessarily -- it won't kill much.

And the thing I think that, you know, it is pretty obvious, is that the HCT/P arena is very diverse. So, we're not really talking about one thing or two things or three things or maybe even 100 things. So, it's very, very difficult to make

any definite conclusions over all of these tissues.

And maybe, you know, one thing that'd be very helpful, is to try to categorize these things in terms of risk, of which processing is one factor, the type of tissue is another. But I don't know, maybe the panel can comment on whether that's been done in their respective fields in terms of trying to stratify the risk by type of tissue and processing.

DR. MACSAI: Well, we can't really cryopreserve the cornea or kill the endothelial cells, so that's out. But we do think that with processing and rewarming tissue, we may allow fungi to reproduce. Hence, antifungals may be better. But there's no processing that I'm aware of or preservation that I'm aware of that would inhibit virus or prion particles.

DR. KUEHNERT: Wait, as far as risk stratification, is there actually a transmission risk stratification concerning bacteria or fungi for corneas, in terms of how long they're stored

or how they're rewarmed?

DR. MACSAI: So, there is one study that looks at, does processing increase the risk of fungal contamination? And that study said no. And now, there's another study that says maybe.

So, we're in, you know, a constantly evolving knowledge base, trying to figure it out.

There are different ways to preserve the cornea. Outside the United States, organ-culture media is done. Wherein the United States, cold-storage media is done. And even in those situations, where there's more time to culture the cornea and look for bacterial and fungal contamination, there's still postoperative infection that's occurring, if you look at the US type data and the European Eye Bank Association data.

And that becomes a very complicated issue because the recipient is not sterile and the environment in which the transplant's done is not sterile.

DR. EASTLUND: Let me ask a question

about the organ culture, the culturing of corneas and using them weeks and weeks later. Don't they use high concentration of glycerol? I'm not sure if they do or not. And if so, that's got antibacterial and antiviral properties.

DR. MACSAI: Do you mean in the organ storage media?

DR. EASTLUND: Yeah. Yeah, cause they must store it at 37 or I'm not sure how -- what --

DR. MACSAI: I'm going to have to plead some ignorance about that. I don't want to misconstrue.

DR. KUEHNERT: Okay.

DR. MACSAI: There's glycerol in all the media.

DR. KUEHNERT: Okay, we're out of time, I think. Is there --

MR. BRUBAKER: One more.

DR. KUEHNERT: One more. Okay, great.

DR. PELTIER: Linda Peltier from McGill University Health Center in Montreal. Looking at preservation methods and transmission, when we

talk about transmission, it's really long before that step. It's not at cryopreservation. I think it's more at screening level and at the donor screening, that we will have to put our, or more, energy for them because when it's cryopreserved, we're doomed already. And in the freezer, if it's liquid phase, we're doubled doomed if the bags are not double bagged.

So, I think that we have to think prior to that, which is probably the introduction of the next section. But I think that we're too late on the preservation methods.

DR. KUEHNERT: Stringent donor screenings. Good point. Any other last comments? Okay.

DR. MILLER: I would just add to that, just really quick. Add collection methods in the middle from where you are to the preservation as well. Because we know the collection method impacts it too. If we look at marrow cord blood and (inaudible).

DR. KUEHNERT: All right. Thank you to

the panel.

(Applause)

DR. FISHMAN: Hey, Matt, is that yours is that -- nope. We're ready to move right along?

So, while we're waiting for the next bunch of slides to appear. I love it when it happens. I'm Jay Fishman from Mass General. My expertise is really outside this entire area, so I have no biases. Xenotransplantation, solid organ, bone marrow transplantation, clinical and research.

So, I think we're going to have a very interesting session on screening and testing approaches. So, the last series of questions were directly relevant. And our first speaker is Michelle McClure, our host. Thank you.

DR. MCCLURE: All right. So, I think that last question that we had for the last session, leads up to this very nicely, as this session is really designed to focus on some of the issues surrounding our screening and testing approaches themselves.

So, my intent for this talk is not to do some regulatory, you know, typical FDA regulatory talk, but rather just to provide a little bit of information to set some background for the rest of the talks in this session.

So, I'll discuss a little bit about what the traditional approach to donor screening and testing is currently. I'll provide some information about cell and tissue claims for donor screening tests and really, what those mean.

We'll discuss a little bit about screening versus diagnostic tests. And also, probably a little bit of information about our current use of multiple types of tests.

So, you saw some of this in an earlier talk already. But this is really what set up our approach that we currently use for donor screening and testing.

So, in FDA's regulations, we say that, you know, for every donor of HCT/Ps, you have to do a donor eligibility determination. So, what is that?

The donor eligibility determination, or the DE determination, is based off of screening and testing of the HCT/P donors for relevant communicable disease agents or diseases or RCDADs, as we've been referring to them. DE determination is required for all donors of HCT/Ps with a few exceptions. And an HCT/P must not be implanted, transplanted, infused, or transferred until a donor has been determined to be eligible, again, with a few special exceptions.

So, when is a donor eligible? In order for a donor to be considered eligible, you have to complete your donor screening and donor testing.

So, donor screening must indicate that the donor is free from risk factors for or clinical evidence of infection due to any RCDADs. And, also, the donor is free from communicable disease risks that are associated with xenotransplantation.

And then the test results for relevant communicable disease agents or diseases, must be negative or nonreactive with one exception for a

nontreponemal test for syphilis, in which there's additional testing that can be done.

So, for screening, we say that you have to, to screen for these risks, you have to screen or review relevant medical records.

So, what are the relevant medical records? FDA considers these to include a current donor medical history interview. A current report of the physical assessment or examination. And then other records if available. Those other records might include: Additional lab test results beyond those that were required, other medical records, coroner autopsy reports, or any other information that might come from a relevant source. For example, there are some cases where relevant information may be found in a police report.

So, what are the general testing requirements? Well, we say that you must -- by FDA's regulations, you must test a donor specimen for evidence of infection due to communicable disease agents. The test must be performed using

appropriate FDA licensed, cleared, or approved donor screening tests, with the exception for chlamydia and gonorrhea, for which there are no screening tests licensed. And so, instead, in our regulations, we provide some information about specific types of diagnostic tests that can be used instead.

In all cases, these tests must be performed in accordance with the manufacturer's instructions for use. And they must be performed in a CLIA certified laboratory or in an equivalent as determined by CMS.

So, some additional information about these screening tests: As I pointed in the last slide, FDA's regulations state that you must test a donor specimen. However, it doesn't actually say that you have to test a donor blood specimen.

But all the screening tests that are currently available are designed for use with blood specimens. And part of that really stems from the fact that a lot of these tests are being designed for use to screen blood donors. And then

being, you know, some additional information, studies being performed to then include tissue donors as well.

But, of course, the blood donors are the big market and are really the focus of a lot of the test manufacturing companies.

So, when we're dealing with HCT/P donors, we've got two different types of donors: We've got those from whom your specimen could be collected. You've got your living donors. So, obviously, their heart's going to be beating when you collect a specimen. And then you also have donors who would be considered -- are deceased donors, but you could still collect a blood specimen for testing before that donor's heart has stopped beating.

So, in either of those cases, if blood is collected while the donor's heart is still beating, then we say that you can use a test as labeled for living donors. And this includes tests that are labeled specifically for blood donors. Even if they don't have that additional

language about living donors, we will consider these acceptable.

On the other hand, if blood is collected after the heart has stopped beating, then you must use a test specifically labeled for cadaveric specimens instead of the more generally labeled test, when applicable and when available.

We have had some, you know, some time points in the past where those tests with that special cadaveric claim just weren't available. And until they became available, people performing the DE determination were able to use a test labeled for living donors. And the reason for this is that once the heart stops beating, there are changes that occur to the blood. And this can affect your test results. And you'll hear a bit more about this in one of the talks later in this session.

So, what other set of requirements are for the so-called cadaveric claims? And I wanted to make sure and put some of this information in there, so that people understand what having that

additional claim actually means.

So, we have a guidance for industry to inform people of the types of studies that we recommend in order for them to get this additional cadaveric claim on a screening test. This guidance is written with a least burdensome approach, and it includes recommendations for sensitivity, specificity, and reproducibility studies.

At least for the sensitivity and reproducibility studies, these studies typically involve specimens that are spiked instead of natural positive specimens.

The requirements, like I said, it's a least burdensome approach. So, we recommend a minimum of 50 specimens for the sensitivity and a minimum of 50 specimens for the specificity studies. Again, these are just minimums.

And then for the reproducibility study, it's a minimum of specimens but with multiple repeats since the goal there is

really looking at the reproducibility of

testing that specimen.

And in all these cases, we compare the results of those specimens, of data collected from the specimens, to data collected for living donors.

And another thing to keep in mind is that these cadaveric claims, these are not stand-alone claims. In order to get this cadaveric claim, you have to also have your test license cleared or approved for screening of blood donors. And there are many, many more, much more extensive studies that have to be done to get that initial blood donor, living donor, screening claim. And so, this is sort of in addition to that claim.

So, and I know in the morning session, during the discussion, there was a little bit of information about the screening versus diagnostic tests, but I'll repeat some of that again here.

So, in general, when FDA approves or clears your license to test, we look very carefully. And the language that's in that

intended use is very particular. And so, tests will be labeled as either screening and/or diagnostic tests. So, for example, a screening test, you might see the statement: Intended for Use as a Donor Screening Test. Or for a diagnostic test, you'll see a statement: Intended for use as an Aid in Diagnosis. Or it'll be something similar to that, that you'll see.

And it's important to keep in mind that these are different. There are different study requirements that companies must do to get one of these claims. For example, some of the stuff that was mentioned already earlier today is, for screening tests, there's a higher emphasis placed on sensitivity. We want to make sure we're not missing any infected donors. However, that also means you might have a higher false positive rate than you have with some of the diagnostic tests.

The populations that these studies are done in are also different. For screening tests, you're dealing with an asymptomatic, very low prevalence populations. The majority of your

donors are not infected, but we're testing them anyways. However, with a diagnostic test, you're using that test because you have some reason to suspect that that patient might be at risk of having a disease. So, they are a little bit higher risk.

And also, just as regulatory background, the screening tests are regulated by CBER. And these are usually handled as either a biological license application, a BLA, or as a 510(k). So, they are cleared or licensed. Whereas, the diagnostic tests are handled by CDRH, our center for devices. They're regulated as medical devices. And so, usually, regulated through the PMA or 510(k) pathway. So, they're usually called either approved or cleared.

And another thing about the diagnostic tests, is that while I said that currently, all donor screening tests use blood as a specimen, that's not necessarily always the case with the diagnostic tests.

So, some other information about these

different types of tests: We know that, in some cases, we might need to conduct more than one test in order to adequately and appropriately assess or test for a single communicable disease agent. So, these might be a NAT, a nucleic acid test. And that test, something such as a PCR or TMA or some sort of serologic test.

And this is really to account for the different phases of infection. We know that for each disease, this looks a little bit different. The period of viremia will be longer for some and shorter for others. And the amount of overlap that they have between when you can detect the nucleic acid itself in the blood versus when IgM or IgG becomes detectable, will vary. And they create different window periods as well.

So, the need for one versus multiple types of tests may not necessarily be the same for every disease or every agent that we're testing for.

And I won't go through this, but I just put this here as an example of, currently, some of

the types of tests that the FDA recommends in cases where, you know, you can see that some of the chronic disease are those that we tend to have recommendations for more than one type of test, cause it's a bigger period that we're having to assess for.

All right. So, with that, I'll let the rest of the next speakers come up. For the rest of the session, we're going to talk about, we're going to have two speakers come up and discuss the reliability and utility of donor screening approaches. We'll have a talk to discuss the -- my slide is disappearing. So, we'll talk about from one of our testing labs to talk about their experience when using cadaveric blood as a specimen for testing. And then this will be followed up with a talk about pathogen persistence and infectivity in cells and tissues using everybody's favorite at the moment, Zika virus, as our example.

Great. Then I'll turn it over to the next speaker.

(Applause)

DR. FISHMAN: So, as you've heard, our next topic is covered in a duet by Dr. David Gocke and Jennifer Li. And Dr. Gocke will come first.

DR. GOCKE: Thank you, sir. Good afternoon everybody. I'm kind of happy to be here and listen to this interesting exchange of ideas and congratulate the staff for - - the FDA staff for putting this thing together.

So, my job is to talk about the correlation, if there is any, between risk behaviors with the development of viral markers in tissue donors. And that will bear on the question or the issue of the reliability of the medical social history.

Here's an old study that we published about 10 years ago, in which we looked at the risk of cadaveric tissue from donors who used non-injected illicit drugs. You may, I'm sure, know that the FDA rule says that one must exclude intravenous drug users or injection drug users. But we were bothered by the fact that we saw many

donors who were using illicit drugs; cocaine, PCP, other things of that sort. And we knew that their behavior patterns would be very similar to that of intravenous drug users.

So, we wanted to know if there was a difference. And sure enough, in over 12,000 donors, we found that about nine percent of them, with a history of non-injection drug use, were seropositive for one or more of the infectious disease markers. And that was compared to only about four percent of the donors who lacked that kind of history of non-injection drug use. Of course, that had very poor positive predictive value. But it did lead us to question ourselves about the suitability of accepting such donors. And MTF chose to decide not to take these donors even though they were not excluded by the FDA rule. We thought it was the right thing to do. It costs us eight or ten percent of the donors out there, but that's what we did.

Going forward, we wanted to further explore the question of the reliability of the

med/soc history, and ask the question of just how reliable is that med/soc history in identifying unsuitable donors. And to be more specific, which med/soc history risk factors could possibly predict, or could have told us in advance that this donor was likely to turn out to be HIV or Hep B or Hep C positive.

So, we did a little study in which we correlated the presence of these risk factors with sero and NAT positivity. And I want to point out here, that now I'm talking about the era, we've advanced to the timeframe when NAT came in to widespread use. So, I'm talking about donors tested, both for antibody and NAT. The previous study I referred to was just serological positive.

And this is in recovered donors. In other words, these were donors that we perceived to be suitable for recovery. We wouldn't have gone ahead with the trouble of taking them in if we didn't think they were going to meet the FDA and AATB guidelines.

And we compared the med/soc risk factors

in 353 donors who turned out to be positive for one of the big viruses, with 340 who turned out to be sero or NAT negative. And these were matched by age, sex, and region of the country. We didn't draw all the donors from a region that would be high incidence of this or that.

And here are the factors that we looked at. And this is where I have to apologize because I'm going to skim over a lot of information, that you need to understand the definitions in these categories. For example, on the left, you look at tattoos and body piercing. If we rejected donors because they had a tattoo or a body piercing, we wouldn't have very many donors.

What we're focusing here on is tattoos, for example. What we dwell on is prison cut tattoos, gang tattoos, homemade tattoos. With piercing, we dwell on genital piercing, not just somebody who's got their ears pierced or their nose pierced or something like that.

And then on the other side there, you'll see things like multiple sexual partners. When I

talk about this, I always get the question, well, you old, prude Dr. Gocke, just how many are too many sex partners. And I always respond it's not the quantity, it's the quality that counts.

And then, of course, cocaine. There as you know from what I said already, we've been excluding individuals who had a history of cocaine use of any kind within the past year. But we do have some donors in there where mom said, oh, my boy was good, he might have used cocaine. Okay, I'm an old infectious disease guy, and I've seen thousands of patients with Hepatitis and HIV. And one of the things that you know very soon is that history is unreliable when you're dealing, even with first-hand information with the patient. But now you're dealing with a secondary source of information, the next of kin. And think about it, the next of kin often don't know or they have good reason to conceal or deny the facts. So, the history is very unreliable.

And here are the results, summarized in red. These are the factors that jumped out, that

looked to be positive to us by chi-square analysis. Some of you may not be happy to see marijuana on the list, but wouldn't be surprised at many of the other things. Cocaine still lights up history of intravenous drug use more than five years ago. Ethanol abuse. Well, ethanol is a drug, and individuals who have a drinking problem, are likely to have other behavioral problems as well.

So, that's the way it's sorted out. And I know we could spend more time talking about the definitions and talk about the numbers and frequencies, but I'm going fast because the time is limited.

Reliability of the source. Well, we noticed that in cases in which the test was positive, sero or NAT was positive, less than half the time was it from a spouse. And down at the bottom there, if you look at the source or the history of being from another person, that would mean a friend or colleague or companion, much more likely to see that in a seropositive case. Again,

back to the reliability of the history.

So, I'm trying to summarize here, basically, what I have to say. We think that about nine percent of donors, talking now about donors who appear to meet FDA guidelines already, about nine percent who have a positive history, med/soc history, turn out to be marker positive. But at the same time, the remaining 90 percent with a positive history, turn out to be marker negative. And on top of that, of those with a negative history, about four percent are marker positive. Such a dilemma, that it's not a very pure cut. It's not exactly what we would like to see.

So, we feel the history is useful in that it helps us to avoid unnecessary recoveries of tissues. We don't like to recover tissue, certainly, not respecting the donors wishes to take it in and then throw it away. And furthermore, it costs money. It costs us time and money to recover a donor. And we don't like to have a rejection. So, the history is useful to

avoid unnecessary recovery, but it certainly is not sufficient to assure safety of the tissue.

Now, thank God for NAT, my superhero of NAT appeared at a time in history. And we have looked at how the serology and NAT tests perform and compare. This was over 10,000 donors done in the recent era, around 2013-14.

And you see at the top, there, that obviously, 92 percent of them were NAT negative, seronegative. And there were a few who were both NAT positive and seropositive, only about.03 percent. A somewhat larger number who were NAT negative but seropositive. I would interpret those as probably representing a remote infection, seven percent.

And then, here are the ones that I'm glad we picked them up, but they puzzle me because there are a few patients who are NAT positive but seronegative. Ones that we would have missed before.

When I ask myself, when in the days before we were doing NAT testing, why didn't we

see more cases of HIV or Hepatitis associated with transplantation of organs. And I digress, but we could talk about that separately. But anyway, NAT does help.

Now, I don't think I have time to really get in to what we're doing now. There is a sore point of my own here that I will breeze through and touch on for the sake of my FDA friends. We're looking at why we reject. And the largest number of donors that we reject are due to Hepatitis B. And if you look at, what did I say that's about over 60 percent of them we reject because of Hepatitis B positive tests. Now, to test B positive, would be either a NAT test for Hep B or would be Hep B core. I happen to think the core is an antiquated test. And here on the left, you notice, in the bar, that eight percent of the Hepatitis B donors had a positive NAT for Hepatitis B. The remainder, we're rejecting because they have a positive core. And the FDA requires us to do total core. If we were to do any IgM core, we would save the majority of those

donors. And I submit, there's a lot of good donors that we're missing or wasting on because of this anachronistic test.

So, let me conclude this sad tale with just a comment about the layers of safety. And I think you've heard this from previous speakers already today. Tissues which do not contain viable cells, the screening, the DRAI, or the med/soc history or whatever you want to call it, and sero and NAT testing and the processing, especially the processing, certainly makes the tissue safe. I have confidence with that. But tissues that contain viable cells that cannot tolerate harsh treatments, we're left to rely on the DRAI and on the sero and NAT testing, which means that one should be very careful about selecting appropriate donors. So, thank you very much. (Applause)

DR. FISHMAN: And to move on to Dr. Li, covering the second half of the same topic. Please.

DR. LI: Great. Thank you so much for

having me this afternoon.

That segues well into to my talk, I think. I was asked to talk about some of the challenges regarding screening of ocular donors. I have no financial interests.

So, as we've already heard, from the last speaker, screening of ocular tissue is probably similar to screening of a lot of the other tissues around. Serologic testing, medical history questionnaire, full-body examination, and of course, an extensive chart review.

The EBAA medical standards does have required donor testing. And these donor testings are in accordance to the EBAA requirements, FDA requirements, State requirements if applicable, and other testing requirements of the country of import if outside the U.S.

The donor testing, as we all know, includes HIV, Hep B, Hep C, syphilis, and then other relevant diseases as per each eye bank.

One of the challenges, I think, with testing for ocular tissue, of course, is the issue

of the postmortem blood draw, which I think our next speaker is going to talk more about. From our standpoint, from my banking standpoint, obviously, plasma dilution is a huge concern. And it can affect the results of communicable disease testing.

We do allow for pretransfusion or infusion samples drawn up to seven days before recovery. But a donor is considered ineligible if there's been sufficient plasma dilution.

I think one of the biggest challenges of ocular tissue, of course, is the timeframe within which we have to work. Ocular tissue here in the U.S. at least, is typically stored in cold-storage temperatures, an intermediate-term preservation.

And so, corneas are preserved in a solution that helps maintain cellular viability for about 14 days. I say 14 days, but the reality is if you talk to most corneal surgeons, and I'm sure most eye bankers, tissue is typically placed well before 14 days. I would say most surgeons are looking to have tissue that's probably seven

days or less, for better or for worse.

And so, we've already heard some of the challenges of the postmortem interview with historian. As we've heard, questionnaires really don't provide, necessarily, sufficient information to identify potential risk factors. And this is particularly a challenge in high-risk populations, which is the exact population that we need the most reliable data in. The EBAA has endorsed the use of the eye-only UDRAI questionnaire starting in October of 2014. And we've provided new guidance for eye banks for use of the UDRAI.

The next step for us in terms of donor screening, of course, is the full-body examination. And this is just to look for any signs of HIV, Hepatitis, or other sorts of high-risk behavior. And this is done obviously, at the time of recovery.

And then the final step is really, the extensive chart review process. And I think this is probably the part that, at least my eye bank, finds to be the most challenging. We have to look

at all the relevant medical records, which was already discussed a little bit, but this is everything. This is EMS reports, Code Blue records, ER records, all dictated reports, all medication records, radiology reports; and all orders, progress notes, Is and Os, vital signs. You can imagine the challenge here. In this day now of electronic medical records that are supposed to help all of us, it instead creates massive amounts of paper for people to kind of go through.

And so, we have, with ocular tissue, at least, a short timeframe, with which we have to review all the medical records. Go back and talk to primary care doctors, go back and talk to historians, if there are discrepancies in the records. And all of it has to be done, again, within this timeframe of technically 14 days, but you're looking more at like seven days.

And, again, this extensive questionnaire, medical record review process, there is a real question of reliability in our

high-risk populations. There is required testing, but there are some things that, within that timeframe of 14 days, is unrealistic to test for. One of the challenges that we're having right now is with fungal, fungal contamination of our donor tissues. And there's really no good way to test reliably for fungal within 14 days. All those results would come back after the fact.

And, again, the challenge of kind of going through all of those medical records and re-interviewing the historians or the primary care doctors within the timeframe that's needed for transplantation.

So, those are the big challenges, I think, from the ocular standpoint that comes in terms of screening and testing for our tissue.

(Applause)

DR. FISHMAN: Thank you very much. Our next speaker is going to cover something which multiple prior speakers have referred to, about test performance using postmortem blood. Dr. Prince.

DR. PRINCE: Good afternoon. Okay, some of the things I'm going to cover today are listed here. We're going to talk about infectious disease reactivity rates in postmortem samples. And I'm going to present some information, both from cross-sectional studies and from serial sampling studies. And then we're going to talk about some of the parameters that are associated with false positive reactivity. These include: Post-death collection time and hemolysis. And, briefly, we'll touch upon some possible causes of false negative reactivity, including inhibitors and hemodilution. And finally, I'll just mention one example of test failure that we see occasionally.

This is a representative cross-sectional study from a French group, where they compared reactivity rates in cornea donors to living donors and the general French population. And you can see that compared to the living donor group, the cornea donor group showed profoundly increased reactivity rates, particularly for HIV and HTLV

and limited increases for the other markers.

This was generally assumed to represent false positive reactivity, but they didn't really do any further analysis to distinguish possible differences in the population groups for that.

A more recent cross-sectional study was presented at last years' AATB by Rod Hale from our organization. The study involved a huge number of samples and represents over five- years' worth of results. And he compared living donors to cornea tissue donors and then people making an anatomical gift.

And what Rod did is he broke down the tissue donor group in to those where the blood was collected premortem versus those where the blood was collected postmortem. And you can see that for most of the markers, there was an increased reactivity rate in the postmortem group compared to the premortem group. Particularly, for surface antigen, HTLV, and HBV NAT.

Now, a couple of other things that Rod noted from this study is that the proportion of

samples that were hemolyzed, was greater in the postmortem tissue donor group compared to the premortem group. And that proportion was even higher in the anatomical gift group. He also noted that the post-death collection time was much longer for the anatomical gift group compared to the post-mortem group.

So, this suggests some sort of interesting, complicated, perhaps, interplay between hemolysis post-death collection time and reactivity rates to infectious disease markers.

Now, I mentioned a more direct way to look at changes in reactivity postmortem versus premortem are from serial sampling studies. This study by Wilkemeyer and colleagues, to my knowledge, represents the largest study of this type that's been performed. He looked at samples from 487 cornea donors. And in these sorts of studies, you collect a sample before death and then another sample after death. You then run both samples through your infectious disease markers panel and compare the results for each

individual.

And what they did is, they segregated the group into two different groups based on the post-death collection time. And you can see, if you look over on the right, those where the postmortem sample was collected within 24 hours of death, only had 0.18 percent discordance samples. And all of those represented false positive reactivity.

But over on the left, if the post-death collection time was more than 24 hours, the discordant rate was 6.5 percent, fourfold higher than the less than 24-hour group. And in this group, we say mainly false positives but also, a few false negatives as well. So, this clearly shows that there seems to be some relationship between post-death collection time and increased discordance between premortem and postmortem results.

Now, going back to that French study that I mentioned at the beginning, they did a nice evaluation of their postmortem samples, looking at

the relationship of their reactivity rates in relation to the post-death collection time. And they broke it down into four different groups. And you can see that for the three markers that they're talking about; HIV antibody, surface antigen, and the core, the reactivity rate increased with increased post-collection time, peaking at somewhere after 24 hours. What they also noticed, is that the proportion of samples that were hemolyzed, also increased with post-death collection time. But that increase seemed to happen a little bit earlier than the increases seen in the reactivity rates.

So, they took the next step and looked at this a little further, where they segregated each of their time groups into samples that were hemolyzed versus samples that were not hemolyzed and looked at the reactivity rate. And that analysis showed that the increase in reactivity was clearly linked to hemolysis and not post-death collection time per se. But there is some sort of relationship there because the longer the

collection time is delayed, the more samples are hemolyzed.

So, just to summarize here about false positive reactivity, so this is most likely a surrogate marker of postmortem absence of osmotic regulation resulting in cell rupture and release or generation of factors that actually cause the false positive reactivity.

A lot of leaders in this field, like Marek Nowicki, feel that it's not the released hemoglobin that's responsible for the false positive reactivity, it's something else. What that factor is, is still unclear.

The limited research on physiological differences in premortem and postmortem blood indicates that there's a general reduction in total protein concentration postmortem. But when you look at specific proteins, there's similar levels of albumin, IgG, and IgM. So, again, there's still much work that needs to be done to understand that.

So, studies are needed to identify the

factors in postmortem serum and plasma that's responsible for false positive reactivity to infectious disease serologic assays. And likewise, studies are needed to further investigate postmortem false positive reactivity in NAT assays and the relationship to specimen quality and the time of collection.

Moving on to false negative. As the Wilkemeyer study showed, false negatives appear to occur much less often than false positive reactivity. But it's of a serious concern from a safety standpoint because you run the risk of donor-derived infection of an unrecognized infection, transmission of an unrecognized infection.

So, one of the most obvious potential sources of false negative reactivity would be an inhibitor in the postmortem serum or plasma. But there have been multiple spiking studies using antibodies, antigens, and nucleic acid material. One example of each of those is listed here. And every single one of these studies has shown that

there is no evidence for any sort of inhibitor in postmortem blood.

So, what are the other possibilities? One that we've mentioned before is hemodilution. Hemodilution requires massive blood loss from the donor and transfusion of crystalloids, colloids, or blood products prior to death. Neither one of these alone can cause hemodilution.

Now, titration studies, and those spiking studies that I just mentioned, indicate that the blood would need to be diluted at least 20-fold, to give a false negative result in the routine infectious disease serologic assays that we're now performing. And hemodilution rarely leads to such high levels of dilution. That being said, there are a couple of described cases of false negative results due to hemodilution. These do occur. They're rare.

And the best one described is by Helm, Heim et, al. in HCV. In this particular donor, the premortem sample was HCV antibody positive, RIBA positive. And on that RIBA blot, there was a

clearly visible IgG control band. But in the postmortem sample, which was a false negative, RIBA negative result, there was no IgG control band visible. And that indicates that the postmortem sample, for whatever reason, had an extremely low level of IgG. And the general consensus of the authors was that this was due to hemodilution in this donor.

Just to touch here on a last issue of test failures. In our lab, we really don't see test failures in postmortem blood, with one exception: And that is, we will see, in about two percent of samples, we will get an invalid Ultrio NAT result when it's initially tested due to a low internal control signal.

So, what that means for us, is that we then have to dilute the sample and retest it so that doubles the turnaround time for that particular donor.

What we have found, and no big surprise, everybody is aware of this, is that the vast majority, greater than 95 percent of these

samples, are hemolyzed. Suggesting that, again, there's a relationship between hemolysis and this failed assay. But less than 10 percent of all severely hemolyzed samples give us an invalid result in this assay. So, again, it's not just a simple relationship between hemolysis and poor test performance. There's other factors involved, and we honestly just don't know what any of those factors are at this point.

So, just to summarize: Infectious disease assay reactivity rates are increased in postmortem blood specimens, compared to premortem specimens. Increased reactivity rates are most significantly associated with hemolysis, which is in turn, associated with increasing time between death and specimen collection. Hemolysis appears to be a surrogate marker for cell destruction, releasing unknown factors that are actually causing the false positive reactivity in these infectious disease assays. False negative assay reactivity in postmortem specimens is really rare compared to false positives. But although some

false negative results represent hemodilution, the mechanisms responsible for most false negative results, remains unclear. And lastly, test failures are uncommon but, again, are nearly always associated with severe hemolysis. And that's it. Thank you. (Applause)

DR. FISHMAN: Very nice job of squeezing a lot of information in. Thank you.

Our next speaker is going to deal with the pathogen that I have on my tie today, the Zika virus and pathogen persistence and infectivity in cells and tissues. Graham Simmons. Thanks very much.

DR. SIMMONS: Can I have my first slides please? As you can tell from my title I'm from Blood Systems,

this is going to be about blood transfusion. Biased talk, I'm afraid.

DR. FISHMAN: Do we have his next -- his first slide? There you go. Thank you.

DR. SIMMONS: So, many viruses can persist as either infectious or replicating or

just naked viral nucleic acid in a variety of tissues.

Now, we all know about the chronic infections, but it can occur for many acute infections as well, particularly, West Nile virus.

Today, I'm going to talk about Zika virus and some of our findings with this flavivirus. And it could also happen with chikungunya virus, which can persist for many months in some tissues.

Also, I'm just going to give a bit of background on Zika virus nucleic acid testing and then some of our data and other peoples' data on tissue tropism. And then talk about viral infectivity.

So, in terms of Zika testing, serological tests are probably not that useful for identifying acute infections. However, there are also issues with the nucleic acid testing. Particularly, that in this previous season and probably going forward, even if there are some small epidemics in the U.S., the majority of cases

are likely to be travelers. And because of the travel, they tend to be at the very late end of acute infection. For seropositive, very low viral loads. And so, therefore, can be difficult to detect.

And I'm going to try to talk a bit about this factor that's been mentioned a few times, that a lack of plasma viremia does not necessary equal lack of presence in tissues. Whether that's infectious or not, is another matter.

So, a number of Zika nucleic acid tests have now received emergency-use authorization from the FDA. I'm particularly going to talk about the Trioplex assay from the CDC.

In terms of blood, during the screening at least, there's been two assays which have received FDA EUA. And that's from Roche Molecular Systems and -- this is now out of date, this should be Grifols. And (inaudible) have made a blinded dilution series of the Zika virus and distributed it to a number of participants. And I got results back and plotted the sensitivity of

these various assays.

As you can see, clustered in the middle here, this is several different labs running the CDC Trioplex assay. This yellow line is actually French labs who are running an alternative platform, which is not approved in the U.S., but is approved for diagnostics.

And then, shown in red, is the combined results for the two blood donor screening platforms from Roche and

(inaudible). And you can see that they are significantly more sensitive than any of the other tests.

And as dramatically shown here, in a collaboration we formed with California National Primate Research Center, where they infected two non-pregnant female macaques with Zika. And we followed them for 14 days.

Now, you can see using the standard CDC assay, we can detect the viremia for about five days. This is even shorter if we actually use

infectivity.

In comparison, when we look on the hematologic platform, you can see that it significantly extends the detection window out to days in one animal. All right. It's also been suggested

that Zika virus RNA and infectivity may persist in compartments other than plasma for longer periods. And this includes urine, saliva, and semen, etc. And this is obviously important for non-mosquito transmission mechanisms. But it may also lengthen the detection window for determining acute infection.

And I'm showing a couple slides from Charles Chui and Jean Patterson at Texas Biomed. This is unpublished work that they've kindly shared with me. And it's studies that they've performed in marmosets.

And you can see, as I said, in a serum, the viremia is detected between three and seven days. However, when they look in urine, saliva, feces, and semen, they find, at least in some

animals, they can continue to detect RNA up to 13 or

days. Unfortunately, it's not consistent, that, for example, here for semen, you can see that two out of the four animals failed to have any detectable RNA in the semen at any point.

A (inaudible) with similar (inaudible) persistence in whole blood. We've demonstrated this for West Nile virus and Dengue virus in the past. This is an example of our West Nile virus studies where blood donors who identified index has been West Nile virus RNA positive were involved in follow-up studies.

And you can see that even at 90 days, the majority of donors still have viral RNA detectable in their whole blood samples, in comparison to plasma, which is cleared between 14 and 21 days and from PBMCs, which is cleared between 21 and 30 days.

And we still don't actually know what the mechanism of this whole blood association really is. But one possibility that I would

mention to you is that it may be infection of hematopoietic stem cell precursors. And then they go on to develop and continue to shed Zika virus or flaviviruses. And this, certainly, fits with the half-life of being over 90 days, which is a red blood cell's life.

And we did similarly see this for Zika virus. Again, index of positive donors who were involved in follow-up studies. And at visit four, which is three months, again, the majority of the donors are still RNA positive in packed red blood cells and packed whole blood. Again, in comparison to plasma, which was cleared between weeks one and three, PBMCs, and also various different platelet preparations, whether the viruses quickly cleared.

So, you might say maybe we should swap from using plasma or serum as a matrix for testing to red blood cells or packed whole blood. Unfortunately, that doesn't appear to be the case, that in about 10 percent of donors who we've involved and followed so far, we found that at no

time point did they have any RNA positivity in their red blood cell fraction.

So, to summarize this part, Zika RNA can persist for three plus months in the RBC fraction. And, again, this highlights the fact that a lack of plasma viremia does not necessarily equal a lack of viral RNA in tissue. However, 10 percent of donors, as I said, lack viral RNA in their red blood cell function at any point.

So, now I'm going to talk about some of our studies on tissue tropism. As I mentioned, we had a collaboration with California National Primate Research Center, where they infected two macaques. These macaques no longer had any detectable viral RNA in any bodily fluid at day 10. And we euthanized at day 14 and analyzed the tissues for viral RNA. And you can see, we saw very high levels of viral load up to 107, 108 in some of these tissues. And this included bone marrow. In general, lymph nodes and spleen were the highest levels. And then we also saw pretty high levels in heart tissue, skin, blood vessels,

etc. And then a number of other tissues were lower levels. Various different muscle and skeletal tissues and, also, genitourinary type tissues.

In contrast, in this study from Charles Chiu and Jean Patterson, I mentioned, they sacrificed their animals at day 28. And they found virtually no tissue was RNA positive. This included eye tissue, the heart, liver, lung, etc.

And in fact, only one of the two marmosets had detectable viral RNA in any tissue, and this was in the lymph nodes. So, we don't know yet whether this is due to the different time period or maybe Zika is persistent in tissues but not very persistent and is mostly cleared by day

or if the difference with the marmoset model. We're currently doing more macaque studies where we will leave the animals for longer before necropsy.

We also looked at fetal infection. So, this is a pregnant female who was infected, both by the IV and the intra-amniotic route in order to

guarantee infection of the fetus. And indeed, we saw fetal death at day seven. And, again, you can see that the maternal tissues are very highly RNA positive and so are placental tissues, amniotic fluid, cord blood, etc., and fetal tissue's also very highly RNA positive.

And probably a more realistic model, Dave O'Connor and Ted Golos of Wisconsin Primate Center, performed infection of pregnant macaques as well. Again, this is unpublished data that they were kind enough to share with me.

So, they infected pregnant animals via intradermal route in order to mimic a mosquito bite. And then they left the animals until 10 days before normal term, before necropsy.

And you can see, again, some of the maternal tissues are fairly strongly RNA positive. And despite the lot longer incubation period, in one out of three, the amniotic fluid is positive. And the result was positive in placenta in one of the animals.

And then when they looked in the fetal

tissues, there was a lot lower levels of RNA, but this is probably due to the route of infection and the time period left. And RNA infection was really sporadic. So, one animal had RNA- positive result in the optic nerve. We also saw in the pericardium in one animal and in bone marrow in one animal, etc.

So, this is just a rundown of all the different tissue studies, and that we see very levels and persistence in the reproductive and gestational tissues. We also see high levels in fetal tissues. In our macaque study, we saw infection in muscle and skeletal tissues and in skin. And other groups have shown in vitro replication in various skin cell types.

Also, in ocular tissues, a couple of mouse studies have shown very high levels of viral replication and even transmissibility of infectious virus, one mouse to another.

But all these results really still ask the question of whether this persistence leads to infectivity, particularly after seroconversion

when strongly neutralizing antibodies are present.

In at least one case, again, that we've heard of, that appears to be through, that in semen, you can detect virus by an RNA for many weeks after infection. And in some cases, it does appear to be infectious. There is at least one report of sexual transmission 30 to 40 days post infection of the sexual partner. There's also been infectious viruses being cultured in semen up to 69 days post-disease onset. However, this is obviously an immune-privileged site, so how this can relate to other situations is not clear.

So, we tried to approach this by looking at this disconnect between viral RNA copy levels and infectivity. So, we took RNA-positive human serum from a plasma or rather from a blood donor, who had a fairly high viral load. And when we look in tissue culture of infectious units, you can see that we see about 500 RNA copies equals

infectious platforming unit. We also used a very sensitive

immunosuppressed mouse model. And we've

already had a couple comments about using mice as models. And I'd just like to point out, we're not trying to look at this as a mimic of transmission, more they're fairly test tubes that we're trying to work out the absolute infectivity of them, a sample.

And you can see in this mouse model, we have only 21 RNA copies. It's sufficient for the percent infectious studies. When we tissue-culture expanded the virus, obviously, we get a far higher viral loads and titers. But the ratios actually go down somewhat, between 5 and 10 percent. So, this may suggest that a tissue-culture-grown virus might not be an ideal substitute to use for spiking studies because it really doesn't represent the infectivity of a prime example.

And then, I'd also like to highlight that the in vivo model is a lot more sensitive, at least 10-fold more sensitive than the tissue culture model (inaudible) time.

And then, the highlight really is that

these 21 RNA copies, is clearly far below the 50 percent limited detection of the current CDC RT-PCR assay.

And we're now going on to continue these studies, looking at minimal infectious studies, by returning to the macaque model, which obviously, will be a more realistic model for, in our case, we're looking at human blood transfusion. So, thank you. (Applause)

DR. FISHMAN: And get the speakers to come up front for our few question before we take a break. And before we take questions from the audience I'm going to give Dr. Gocke a chance to talk about something that he alluded to.

(Recess)

DR. FISHMAN: So I had one question to start which was you, like myself, were very with the power of nucleic acid testing as an adjunct to screening and diagnosis. But you raise the question, well, why was in the eras before NAT testing we didn't see more infection? Was it that we weren't missing much or that it didn't matter

or that symptomatic disease was less common?

DR. GOCKE: I'm puzzled by that and I'm hopeful that with all the experts assembled in this auditorium you can help me to understand that. I can think of a number of possible reasons, underreporting, being one. Question is whether-- and this is for Dr. Simmons, how does one tell when you have a positive nucleic acid test that that's infectious? What else, any other? I think that --

DR. SIMMONS: I think a lot of it may be (inaudible) infection.

DR. GOCKE: The number of positives were small and so it may have just been lost in what goes on out there in the busy world. That's the best I can do.

DR. FISHMAN: Other comments from the panel? If not, one question, and I'll let Dr. Simmons start. So we're in the era, I suppose I'm not supposed to say this, but we're in the era of routine nucleic acid testing and the criteria that we use for assays are spiking assays. So let me

be blunt about it, are those useful?

DR. SIMMONS: Yeah. I mean, I think they're useful. You want to try and mimic natural situation as close as possible. So, I, you know--

DR. FISHMAN: Has anyone actually done a comparison between natural infection and spiked assays in terms of the quality of the assays and whether or not they are comparable?

DR. SIMMONS: Yeah. So the two panels we produced, one was a tissue culture spiked virus and the other was the same human plasma that we did in the mice and tested several dilutions in plasma. And there we saw pretty similar levels that the limited detection for the assays was very similar.

DR. FISHMAN: Other comments?

DR. BRAMBILLA: Don Brambilla from RTI. I want to comment on this. I work on the virology quality assurance program which is funded by NIAID to provide proficiency testing, among other things, to laboratories, and HIV research that's funded by NIH. And several years ago we did a

test on one of our proficiency panels in which we put replicate aliquots of patient samples next to replicate aliquots of spiked samples to see what kind of standard deviations we got. We got about the same standard deviation for both of them. And, you know, pretty much performance.

DR. FISHMAN: So I can just add my own experience to that because I developed a lot of homegrown assays and it may be a nature of a homegrown assay, but I don't find that to be the case. And I find that spiked and if you spike into multiple different samples you actually get multiple different results. So that there is some variability there and I worry a little bit about the differences, not one way or the other, but of natural samples versus spiked samples that's why I brought it up. Michelle, did you --

DR. SIMMONS: I would definitely say that for different matrices it may be different. With the positive plasma diluted into the plasma, but then I feel looking at whole blood then that may be a completely different issue because it

didn't, even if the virus is bound to the surface of the red blood cells or it's internalized. So that would definitely make a difference. And I think with semen samples, too, there would be issues with spiking.

DR. FISHMAN: Michelle, do you have a comment?

DR. MCCLURE: Yeah. So was just going to, you know, put in a little plug for, at least for, the screening test that we use. Well, we don't have these additional studies for the cadaveric specimens, but for the initial studies where the manufacture is trying to get a claim just for testing of blood donors and other living donors. There are numerous different types of studies that they have to do and a lot of them are very large studies that will involve some spiked specimens, but there are a certain amount of studies, or some studies that they have to do that involve true, positive, naturally infected specimens. And these are, of course, they're not specimens that are initially collected from blood

donors, but where they will go to collect specimens from a place where, you know, if it's Zika virus then maybe they got their specimens from Brazil or they'll get them somewhere to where they can find a certain number of specimens from an infected donor and include those in the study.

So at least for the screening test for the, for what's done on the living donors there are some requirements there to try to capture that potential difference that's there. Of course, we don't have that for cadaveric donors because I don't think anybody is going to be able to provide us with a supply of naturally infected specimens from deceased donors, but it would be great if we did.

DR. GREENWALD: This is Melissa Greenwald from HRSA, I'll add to that there's a, hopefully, a paper coming out in the near future of some research that I participated in with some colleagues at FDA when I was still there. Where we did obtain specimens from individuals who were infected at the time of death with HIV, hepatitis

B, hepatitis C. Small numbers, because having been the reviewer for some of these assays I wondered the same question. I will emphasize what Michelle said, which was that spiked studies are only the way to get license predicated on having a blood donor screening claim which is very important because I would be skeptical about that being the only way to evaluate an assay.

But what we found in our data is that we were able to detect, you know, analytes, antibody not in the assays from naturally infected individuals. There are some, you know, methodological issues, but it is something definitely to think about and be skeptical about, and, but that it seems to be fairly reliable in being to, at least, make part of the assessment on the reliability assays.

DR. FISHMAN: Other comments from anybody on this topic or questions for our panel? Please.

(INTERRUPTION; OFF THE RECORD DISCUSSION)

MS. SHIER: So coming to you, Quest Diagnostics Nicol's Institute in Chantilly, Virginia. We're receiving an increasing number of requests for donor cornea rim culture, specifically for a fungus, and I was wondering if you could address the clinic utility and the guidelines for this, giving that we do incubate these for 4 weeks before we're able to provide a result.

DR. LI: So in terms of ocular tissues, again, as a clinician, as a surgeon, the biggest concern I actually have is with fungal infection and fungal contamination of tissue. In the studies that have been done in the past, looking at utility of donor rim cultures for bacteria have really not shown that that is a useful practice.

DR. LI: That being said, fungal is different. A fungal seems to be a little bit on the rise for us. It's still a little unclear why. We're kind of looking into that, but it may have to do with some of the processing that we're doing of donor corneal tissue at this point in time.

But we, if in fact, again, if there is contamination from fungal, our media doesn't contain anything to help it, right? So for bacteria we've got the Optisol, it has gentamycin, streptomycin in it and that seems to do a fairly good job. And then, more importantly, for my recipients, my patients, are all getting antibacterial coverage postoperatively as well. Which, I think, decreases their risk of developing an infectious keratitis or an ophthalmitis.

DR. LI: Now, with fungal, there's no treatment, they're not getting any sort of barriers to fungal coverage, postoperatively. And they're also being placed on steroids, postoperatively, it's topically. Which can also increase their risk of developing a fungal keratitis or an ophthalmitis. And so, from our standpoint, from a corneal surgeon standpoint, I think the donor rim culture for fungal is actually the most important. Because if we do get a positive back then we will actually adjust our postoperative medication regimen for our patients

to try and decrease the risk of infection.

DR. LI: Fungal infections of the eye are notoriously hard to treat. And so, the earlier we can get on it, the better. And so, I actually, personally, I culture all of my donor rims for fungus.

MS. SHIER: Yeah. So we do screen, you know, we are screening those on a weekly basis. So if it's positive, it's going to go out, but, obviously, it could take multiple weeks to grow. Depending on the fungal organism, of course. Right, candida will usually recover within a week.

DR. LI: Yeah. And so, again, I'm not surprised that you're seeing more requests for that just because it is becoming more prevalent.

DR. FISHMAN: Can I just ask -- we'll get to you one second. Have you thought about using other screening, nonculture screening methods like a glucan test for your culture media or for your corneas so that we don't have to increase the random use of antimicrobials in our population?

DR. LI: The random use of antimicrobials in our population. Sure, we should look into that. (laughter)

DR. FISHMAN: Sorry, I'm an ID guy, so, you know, it's like --

DR. SIMMONS: Well, you know, unfortunately, an ophthalmologist, I'll be the first to admit a lot of what we do, you know, the only thing that has been shown to effectively decreases the risk of postoperative and ophthalmitis for our eye patients is the prep. I mean, so most of what we do is --

DR. FISHMAN: Yeah, way better than calling me afterwards. Yeah.

DR. SIMMONS: Yeah.

DR. FISHMAN: Please. DR. Kagan: Richard Kagan from

Cincinnati. Has there ever been a study done in organ donors who later became tissue donors, shortly thereafter, looking at the premortem blood sample that was obtained with a postmortem blood sample taken at the time of the

actual tissue recovery?

DR. GOCKE: Richard, I think Dr. Kagan raises a very worthy point because I think it's a missed opportunity there. We have not a lot, not all of them, but there are matching tissue and organ donors where we have an opportunity to do valuable research and I think it's good that you brought that to attention.

DR. HANLEY: Patrick Hanley from the International Society for Cellular Therapy and also down the street at Children's National. So, I think it was you actually, you mentioned that there was false positives with the hep core, hep B core, and we are moving more towards NAT testing. But my question is, are we going to be moving towards NAT testing for all pathogens, all viruses or, you know, what do you guys think? Because we do find it simpler if it's all NAT or all serology rather than NAT for this and serology for that.

DR. GOCKE: Well, I don't know quite how to answer that. I think you pose an economic and financial question there which goes beyond strict

scientific answers. I suppose you could say it would be entirely logical to do just NAT testing. I don't think we're at that point yet.

DR. FISHMAN: Wouldn't that depend to a certain extent on the pathogen though in terms of the timing of the serologic versus the nucleic acid response. So in some it's been shown that they are not mutually exclusive that they are -- it's beneficial. West Nile is the one that comes to mind for screening tests. So I don't think you're going to get off the hook that easily.

DR. GOCKE: I think when you're -- what comes up is not just in the initial screening, but the follow of that patient. It may be more useful to follow the antibody tighter than to follow the NATs.

DR. FISHMAN: Other comments from the panel?

MALE: A question about qualifying the assays for licensure for the tissue donors in particular. One of the most difficult requirements is the reproducibility studies

because you're requiring 20 replicates in and the volume of sample that's obtainable from cadaveric donors is, generally, prohibitive for such things. Do you see some flexibility in trying to get around where sample access is a problem?

DR. MCCLURE: Yeah. So when you're looking at reproducibility, it's really looking at, you know, getting those same results over and over. And so, while, ideally, we would use the same specimen to do all those replicates, however, sometimes that is a limitation with cadaveric specimens. So in those cases there is potential, you know, maybe create some pools of the specimens for testing and use those same -- make sure and use those same pools of maybe two or three different specimens to do that, to do all the replicates.

DR. MCCLURE: And it's something that we've always -- when there's been issues it's something that we've, you know, FDA tries to work with the manufacture to get around it, so that we can make sure and get the data that is needed.

DR. STRONG: Jay, I have a question for you. Since you're a pig guy, you so proudly have proclaimed. Mike Strong, Seattle, retired. I'm curious about it, what your thoughts are towards the recent dramatic success with human- pig chimeras and its potential for emerging infectious disease from that model?

DR. FISHMAN: So just to -- for background for those who didn't read the non-lay press reports of pig-human chimeras. We don't really have organs being produced that can be used for transplantation yet in these. And the prospects are kind of modest. That said, and you could certainly talk about various ethical issues that I won't go in to right now, the idea that there would be transplantable tissues, organs, whatever coming from pig-human chimeras doesn't overcome the main infectious disease barrier to porcine transplantation which has been the porcine endogenous retrovirus. Which, by way of disclosure, I cloned and patented it. So, I'm not sure it's a huge advance from that perspective. It

may be in terms of availability, but's it's not like we're short of pigs for, as organ donors who are the correct size or skin donors in the like, so I don't know if it's a major advance, yet. I think that, and I think my guess is that the ethical issues are going to come fast and furious before the infectious disease issues. And that said, there have been no human studies that suggest that this virus, which has been inhibitory for xenotransplantation is actually infectious for humans. So it is in vitro for certain human cell lines, but not for intact, normal human cells. So hard to know where that's going to go, but there's a great meeting coming up with the FDA in September on exactly that subject.

DR. STRONG: So what's your prediction for the possibility of these getting to a trial stage?

DR. FISHMAN: The chimeras, I don't think I'm going to be working by the time they come to clinical trials. I'm hoping.

DR. STRONG: Forget about retirement,

I'm here to say.

DR. FISHMAN: I'll be dead by then.

(laughter)

DR. STRONG: Have you signed your organ donor card?

DR. FISHMAN: Yeah, I have.

DR. MCCLURE: I think we're going to let Melissa add one more comment and then in interest of time we might let everybody take a quick break and then come back so that we can get to some of the prepared questions.

DR. FISHMAN: (talks over) Do you want to take a break or do you want to just go right into these?

DR. MCCLURE: Well, I guess that's up to everybody else. We had a break scheduled, but we can skip it if we don't need it.

DR. FISHMAN: Do we need a break?

DR. MCCLURE: All right. Then we'll keep on going. So we'll let Melissa finish this thing, then we'll get to some of these questions.

DR. FISHMAN: We're going to go on.

We're going to be here until 8 o'clock, folks.

(inaudible)

DR. GREENWALD: For the recording, Melissa Greenwald, HRSA, again. For the individual who was asking about pre and postmortem specimens from the same individual when they donate organs and tissues. I actually spent a couple of years trying to design that study. And it turns out when they collect organs that they remove the blood and they're using organ preservation fluid instead to circulate the body. So you can't really get postmortem blood from those individuals. However, with AOPO I worked through their Organ Donation Research Consortium, and it seems like there's a certain percentage of tissue donors that live in New York, you know, did a little mini study over a month for me, you know? And about 10% of their tissue donors, if they went back to the lab they could find premortem specimens from the people they were able to obtain postmortem specimens from. And so, that would be a way to obtain pre and postmortem specimens from

the same individual. And I just wasn't able to get that done at FDA before I left. So someone should do that study.

DR. FISHMAN: There's one more question in the middle. No, no you're not allowed to do it. There are rules here.

DR. SCHULTZ: Dan Schultz from Tampa. I work for an OPO as well as a tissue bank. And one of the sticky points on the OPO side is, obviously, they've done their testing on the front end and then if you were in the back end subsequently do a second, a repeat. It's different when you're talking about their initial testing, but if they do screening tests and you repeat it, the fear is obviously you're doing another test. And they're going to have to deal with that result. Likewise, if you had released tissue and someone decided later to send out a specimen and get new news. You then have to deal with it, and, in fact, it may be just completely artefactual because of that specimen. So that's another thing to keep in mind coming from the OPO

perspective on that. But if you could do it completely blinded, get those specimens. Perfect.

DR. FISHMAN: Yeah. And just to comment on that, and I don't know if Matt wants to comment based on his experience. But when we looked back at the discordance between, and the same donors between testing there was a certain amount of discordance. And it didn't go one way or the other, as I recall. Matt may recall better than I because he's much younger, but his idea was that this retesting, and there wasn't a mechanism for communication of results between the tissue and the organ communities, and blood, I should say, which is unfortunate. And I think that is a clear opportunity to increase the safety of all the things that we transplant because this redundant testing may have a benefit, but it's only a benefit if people know about the results. So let's go on to the discussion panel because Michelle worked very hard at putting together these questions before we started. And the first questions is --

DR. MCCLURE: I will say that was a whole group of people, including our representatives from AATB, EBAA, ASRM, NMDP. We thank them very much.

DR. FISHMAN: She worked them very hard at making us try to answer these before we got here. (laughter)

DR. MCCLURE: Make sure they get credit, too.

DR. FISHMAN: This is about accessing the blame, not credit. (laughter) Are there improvements that could be made in the traditional donor screening and testing approach as to better protect public health? And this is about the issue of traditional donor screening and the increased heterogeneity of diseases, tissues, and donors. So let me turn it to the panel. Basically, can we improve the way we're doing testing now, and if so, how? And with talking about the diversity of tissue types as well as our donors.

DR. GOCKE: Well, I think as I -- the

point I tried to make in my talk was that we need to learn a lot more about the reliability and usefulness of donor screening methods, both historical and testing. And so, yeah, the answer to your question is, yeah, we need to do more work or research. Exactly how that's going to go, we are trying to look at it in terms of identifying the reasons that we reject donors. Could we have predicted that? Could have done a better job?

I think the testing is a another aspect of this whole process and I was going to say I was a little astounded by my new friends, Dr. Prince's comments on the false reactives, about the effect of hemolysis on the test results. Can we improve - - could we make improvements in how we handle a specimen, storage, transporting, centrifugation. Simple things like that, that could play a role. So I think we have more work to do.

DR. FISHMAN: Dr. Prince?

DR. PRINCE: Yeah, I can say this because I'm the lab guy and doesn't affect me, but, you know, if there were any way to increase

the -- well, decrease the time between death and the collection of the specimens, it's going to cut down on hemolysis, and, not only the time. It's using the right gauge needle and using the right collection tubes and getting it into centrifuge as fast as you can, would go a long way, I think, to improve in the quality of the specimens that we have to work with.

DR. FISHMAN: Other comments from, Dr. Strong.

DR. STRONG: Mike Strong, Seattle, retired. In that regard, there were some techniques developed to remove hemolysis from lab samples. And I wondered if you have done any studies looking at those techniques to see if it has any effects on the outcome of the test?

DR. PRINCE: I have to plead ignorance. I'm not aware of those studies that you can do to remove hemolysis. That would be really interesting to see. I've always wondered if there's something you could add to a hemolyzed sample to neutralize the false reactivity and

things. And so, it's sort of along those same sorts of thought processes.

DR. STRONG: Well, there were studies published -- well, I have to confess, I've been retired for ten years. So these would have been studies published more than ten years ago. But it always intrigued me that, that would be an approach. The problem is the sample size. We don't have enough samples or enough samples to get those studies done. But it seems like one place where we can remove hemolysis. And I do think there are inhibitors. The studies that we did back in the early 2000s with nucleic acid tests, there clearly were the inhibitors which you could remove by simply diluting a sample, one to two. So --

DR. PRINCE: Right. And that's what works with the NAT now. We get an invalid NAT result, we just dilute it one to five, and we always get a result.

DR. GOCKE: You know, we're touching here on a big difference between the real world

and the nitty gritty of recovering a donor and requiring a tissue versus what best possible approach might be. And I don't know, I understand the importance of what Dr. Prince says. But, you know, we're trying, when a person dies and you're trying to get permission to recover that tissue, there's a rush to assemble the necessary information and data within a short period of time get the tissue recovered and often in the middle of the night. So and with a team of recovery technicians who may or may not be sensitive to Dr. Prince's requirements for how the blood is collected. So there is a difference between the real world and what we would like it to be, Mike.

DR. PRINCE: That's why I said I'm just a lab guy. I know that it's much more difficult out there in the real world than it is in my little lab.

DR. GOCKE: But Dr. Strong is going to tell us how to work on that problem. (laughter)

DR. FISHMAN: Matt?

DR. STRONG: Well, this is just more of

a disruptive question related to number one here, which is that, remember, there was an FDA workshop a few years back on advanced molecular testing, focusing on next generation sequencing. And this is something that, I remember, the blood bankers in the room kind of had a panic attack because you know that actually every donor is likely going to be positive because you've got all sorts of, sort of the human genome in your blood. But this might also solve sort of the some of the issues concerning, you know, questionable results concerning nucleic acid testing, serology. You just replace it with some sort of algorithm to discern all the results on next generation sequencing to the things that you're interested in. And presumably, shield yourself from the results, from the results of the things you're not interested in. And I just wondered if anyone in the panel has sort of looked at that and at least compared NGS versus the serology in that approach.

DR. FISHMAN: So maybe I can take a shot at that one because we've done whole genome

sequencing from macaque samples recently. And one of the things that happened, and you can look at different virologic markers in completely asymptomatic animals, and we found two viruses that have never been previously described. And we actually don't know what to do with them. The reality is, and I'm -- just to build on your comment, which is, the idea that there improvements that we could make in the donor testing paradigm assumes that we know what we're looking for, and I don't know think that we do. And I think, so there's the public health piece which is very important, where we say should we be looking and testing these and looking for anything, any biologic that is contaminating these samples, and then asking what we're picking up. And then there's the piece that you just said which is the ones that we know about that are required by various regulations that we seek. And I think both are important. But I think the -- I would answer the first question, is that we don't know what we're missing, and, therefore, it's very

hard to say how we can make improvements or which assays we should deploy. Clearly, the comments that you've made are relevant. We have to make the assays that we're using better and make them work better. But that's assuming we know what it is we should be looking for. Um, and so one of the slides had the TTI viruses on -- well, they're wildly increased in any abnormal or immunosuppressed host. We don't know what they do. They're an interesting marker, but we all carry them. And yet they're not excluded, I hope, by anybody's regulations which we don't even know if they cause disease. But there are going to be a lot of new pathogens that we're going to discover, and I don't think we're looking hard enough.

DR. SIMMONS: So, I'd just like to say at BSRI we have performed a lot of fellow discovery work. And, in general, blood donors are actually pretty clean. All that's needed is the GNLA viruses, but we really found any interesting on level viruses from blood donor populations.

DR. FISHMAN: Yeah, and I think that gets to -- I think that's probably right. And I think he gets to the issue of looking differently at semen and at stems and at tissue. And so, we can't put all of these together because the host is different, and, therefore, the demands on the sample are a little bit different. Other comments regarding question one? Please.

DR. SIMMONS: And in just regarding Matt's question about next gen sequencing isn't really at the sensitivity at the moment to get anywhere in near the blood screen platforms. There are people such as, APA Diagnostic (phonetic) in (inaudible) working on specific target capture prior to the next gen sequencing. But they may yield good results in years to come.

DR. FISHMAN: Okay, to move to the next question which I've think we've dealt with fairly nicely. But how reliable is the use of behavior history for a living and deceased donors in the

absence of an available test. We're using available tests. What we've heard is the donor history is useful, but not exclusively useful. Any additional comments that anybody would like to make about it?

DR. SIMMONS: No, no. I --

DR. GOCKE: I tried to make that point very clear. It's not very -- it's useful for us, only in a -- we don't like to recover tissue and then throw it away. But it certainly doesn't prove the safety of the tissue.

DR. MCCLURE: I mean, it's -- in some ways what we have to work with, right? So there's no getting around it, but --

DR. FISHMAN: I think there is, though, another aspect to this which is that we haven't refined out questionnaires or examined the way we use questionnaires, and is there a way we could do them better? And I'm just asking that in the sense that we have donor questionnaires. We keep using them. Aren't you retired? (laughter)

DR. STRONG: Mike Strong, retired. I

don't -- you know, I don't, you know, I don't go to these meetings anymore. So I have to make up for questions. Actually, the blood folk have this question on their plate for 20 years as to the validity of the donor questionnaire. And I know in BPAC meetings in the past that we have discussed with the behavioral scientist how to best test the questions that are on the questionnaire because you're dealing with different ethnic groups, who have different understandings of what the questions might mean. And I think one thing that would be very useful in this population would be to engage some of the behavioral science people who developed this kind of work and know how to test them to look at validity and efficacy of any of the individual questions that we ask because some of them are absolutely worthless.

DR. FISHMAN: Is that -- oh, please, in the back.

DR. PELTIER: Linda Peltier McGill University

(inaudible). On the behavioral, I'm (inaudible) that's, now you know. History, should we also, there's some countries who started also to ask, not only the donor, but the companion of the donor so that we have a better and history and behavioral history of it. So should we start not only asking the questionnaire to the donor, but also to his companion or her companion? Would that increase or increase the quality or decrease the risk of transmission?

DR. FISHMAN: I don't know that it's been studied, um, there is the time limitation and the confusion around consent, which is, the question are you asking people who are the also the people who are going to be giving consent or are you asking additional people? There are ethical issues as well with that. I don't have any difficulty with it. I understand where it's

coming from, but --

DR. PELTIER: And as for organ donors, I always say, because I work in the Canadian OPO and the donor will always die with what he never said to anyone. So sadly, probably there will be one case that will pop up and we won't ever be able to screen that person or even have the history of that.

DR. GOCKE: I'm sorry I didn't really hear the question. I couldn't understand the question.

DR. FISHMAN: The question is really surrounding about who do you ask the donor questions of and should you be doing more? And that's, of course, a very tricky issue in a variety of ways.

DR. GOCKE: Yes, you know, you don't really -- the effective proper taking of a questionnaire or medical history requires a certain amount of skill and experience and just reading off of a sheet of paper. Did this donor or did this individual do this or that or that's

not necessarily getting a full and complete and reliable history. Now, I don't know how to get around that problem. You can't really have highly trained physicians or nurses who are doing the actual interviews at all hours of the day and night. It's a problem. It's a -- your question is good, but the answer is difficult.

DR. FISHMAN: Please.

MR. REAL: So a -- I think this is on, isn't it? Yeah. Okay, a couple of quick, quick things here. This is Mike Real from MTF. There was some questions about the donor risk assessment interview earlier and standardization, evaluation, and there has been massive amount of work that's been done jointly through AATB, AOPO, and EBAA on a uniform donor risk assessment questionnaire. Not only assessing it, it's -- getting something uniform for all of the different groups to utilize on deceased donor and living donors as well. But also the evaluation by -- and I can't remember the group's name. Scott, do you? NCHS, to evaluate the effectiveness of each of the individual

questions at eliciting the responses that you need to get the information that you need.

So for those of you in the room that don't understand that it's been eight, nine years' worth of work and refinement in getting a very effective tool. The only thing is, it's not required. Now, there's been various adoption --

DR. FISHMAN: When you say very effective, measured by what?

MR. REAL: Well, I think that the -- initially measured by the group that we worked with and listing their response in test groups as to get the -- as you ask them that, are you getting the information you need in order to do that. Now, is it effective in eliminating the need for testing? I think that we all know that that's not true because you're dealing with secondary individuals. You're not dealing with the donor themselves in most circumstance, and so forth.

But it's a much better tool than what we've utilized for many, many years. And the

adoption of it has been very good. I'm guessing that the majority of all the accredited banks, both the EBAA and AATB are utilizing these and I know of AOPO's, are utilizing it as well. So it's a massive step forward from, nobody's using the same questionnaire. The questions aren't effective. They're out of date. That, I just don't feel that that's true from the amount of work that's gone on.

And then secondly, to kind of address Dr. Gocke's comment there. You're right, we can't have trained nurses and physician, but we can have trained technicians and coordinators. And we can spend time with them on how to elicit their response, how to ask the questions so they're not just reading it off a piece of paper. They know what drill down questions to ask. They know, um, how to read people's responses to determine, is it accurate? Do I need to seek another source of information, et cetera? So to answer the question, how you make the -- this better tool that we have more effective is training.

DR. GOCKE: Yeah. I have to agree with my colleague, Mike Real and Bruce or Scott. You know, I don't mean to denigrate (inaudible) but we have come a long way, baby, with regard to that history. But it's still only piece of the puzzle. We still have problems in implementing it effectively.

DR. FISHMAN: So let's move on to the --

DR. GOCKE: The real world is a problem, baby.

(laughter)

DR. FISHMAN: So question three. What approaches -- oh, sorry.

DR. SCHULTZ: One other comment with regard to how we can improve -- Dan Schultz from Tampa, and with the AATB, Chair. One of the other things we can do as an improvement is basically, common sense. And that this, although, first of all, if we have a person who is an authorized donor, they're on the death registry, then girlfriend, spouses, whomever, they're all open game for histories because they're on the

registry. If they are an authorized donor, by a spouse or parent, if they give us the okay to talk to a girlfriend, another person who's close to them always optimal. Because the fact is if you ask my mom when my appendix came out she'll know. If you ask my wife or I won't say girlfriend, but, anyway, if you ask they're going to know certain things that the others are not going to know.

And so, in my situation if I find out later that somebody has a girlfriend that showed up in the ER, yet the parent did the history, I always ask to talk to the girlfriend. And we try to get that, now, sometimes we don't, but we know and we see that those histories are quite different on the high risk things versus what we get on the medical background.

DR. FISHMAN: Thank you. So what approaches could be considered to prevent transmission of pathogens that are present in certain tissues after the viremia has resolved? Screening tests or other tests that could be applied to cells, tissues, organs, whatever.

DR. MCCLURE: I'm not going to answer that question, but I will start the conversation since no one is jumping in. Obviously, this presentation that we just saw from Graham on Zika virus is a prime example of where this becomes an issue. Where we're seeing infectious virus in placenta or in semen at points where it's no longer detectable in blood, you know? What can we do to better address that because we're also sitting here listening to, you know, people talk about behavioral history as a tool alone is not, maybe is not all that great. So what other approaches can we look at?

DR. GOCKE: Well, the question sort of raises -- the questions poses the question of what could one do to treat the tissue after recovery? You're not dealing with history now. We're talking about some method of inactivating viruses, pathogen reduction type of thing. Of course, beginning in the early days of, uh, the industry we were all preoccupied by about the safety of the tissue. And many tissue processors took up the

habit of frying it with gamma radiation, or doing other forms of harsh chemical treatment. Well, I think there's been a body of evidence that accumulated in the meantime that says this destroys the biological properties of some tissues and it's not the answer. It's not a good thing to do.

So is there something out right now in the blood industry? There's a lot of excitement about pathogen reduction methods. I don't think that can be applied to the kind of tissues we deal with. But, yeah, we need to look for other means of treating the tissue.

DR. FISHMAN: Comments from anyone else? I think it also speaks, though, to the need for research in terms of just the kinds of things you've heard.

DR. GOCKE: Yeah, absolutely.

DR. FISHMAN: In terms of persistence and infectivity of pathogens in various tissues and we know have heard over and over again that it varies by organism and it varies by tissue and we

don't know what else it may vary by. So we don't know that we gain assurance on one organism versus another.

DR. GOCKE: There's a need for funding of that kind of research. I think we repeatedly bump into that kind of issue. One of the questions this morning raised the same thing. And I think what happens is that individual tissue processors don't have the time, resources, and money to invest in the kind of research that's needed to answer these questions. And if they did it would be proprietary information. Okay. So, you know, there's a need for independent funding from a source that's going to get really at the root of the problems.

DR. FISHMAN: Other comments?

DR. SIMMONS: Yeah, I'd just like to back up what you said that it's going to be completely pathogen specific and, you know. And, you know, for Zika, for example, one it's dropped below detection in plasma the (inaudible) are probably pretty low. So, you know, we heard

before that maybe freezing isn't that good of pathogen reduction, but if it reduces it by tenfold, which in our tissue (inaudible) examples it certainly does. And that may be enough. If the (inaudible) stay low.

DR. MCCLURE: And I will follow up with Dr. Gocke's comments. I think that kind of points to another big lingering question that I think we plan to talk about during tomorrow's panel discussion also. And that is, what can we, as a field, do to, you know, focus more on some of these research efforts. I mean, yes, we know that some, you know, private institutions may do some research, but maybe that's not information they're willing to share or maybe they are willing to share it they just need a way to get that information out there or help getting that information out there or, you know, anything -- I think we need to start thinking about what can we as a collective field do to improve the research so that we have better tools and resources available to us.

DR. GOCKE: I would say amen to that. I think

(laughter) I would love to see a REDS type study done in the tissue industry. And I think the TODES study attempted to blaze the trail here. But maybe this is one of the beneficial effects of having a meeting like this where you bring participants from different aspects to get together and start thinking how could we collaborate. For example, I think many, some tissue banks, tissue processors would be glad to help collaborate with test developers to develop panels of specimens.

There's opportunities like Dr. Kagan raised about mapping donors that are both organ and tissues donors. I think we need to come together. I agree with that.

DR. FISHMAN: Other comments? Okay.

We've touched on this, I'd like to change it just a bit. What measures can be taken to improve test performance in post mortem blood specimens? And the question I would ask for my lab jocks, are really are there controls that we could introduce so that we would know whether or not specimens were suboptimal, in other words, could we modify. You talked about hemolysis and the fact that perhaps it wasn't hemoglobin. Is their research going on or are there tools that would allow us to assess the viability or value of individual specimens?

DR. PRINCE: Not that I'm aware of currently. And I that would be my recommendation as part of these last few questions is that another area of research is to identify whatever these factors are that's responsible for false positive and even false negative results. Assuming that it isn't hemoglobin which seems to be the case. How do you go about that? I don't have a good handle on that, but as far as today there's no way we can tell exactly which hemolyte

specimens going to be fine and which hemolyte specimen's going to be a problem.

DR. FISHMAN: Yeah, I mean, to that end I was impressed by your data suggesting that in vitro versus in vivo isolates used in spiking studies were different. And one might not have assumed that although we know, for example, for some common viruses like cytomegalovirus that the strains that have been carried and used routinely in lab assays are not the clinical strains anymore that they have deviated over time. So they lose genes over time. So that shouldn't be terribly surprising, but we keep rediscovering that. So, okay, and what can do to increase the availability of donor screening tests labeled specifically for testing specimens in the post mortem? I don't know if we still have our industry representatives here, what can we do to make more palatable, more common, more frequent, and from my panel?

DR. MCCLURE: Well, I think our friend from Roche has left already. I don't see her up there anymore. But one thing I'll start out by

saying is one topic that's been brought up already is about tissue establishments helping to provide panels that these test kit manufacturers can use for testing. Another thing is also just communication among the end users to those test kit manufacturers.

We tend to, in the tissue field, we tend to kind of ride the coat tails of the blood field. But the blood -- the test kit manufactures don't just predict what it is that the blood field's going to need. The people in the blood field, they are communicating constantly. They have very close relationships with these test kit manufacturers. And that's how they communicate their needs. And so that way the test kit manufactures can try to be prepared, you know, as prepared as possible as new diseases are emerging or as there's a new need for testing.

So I think, just my general comments, there's a couple things that I think there's some, some lessons we can learn from that field and kind of being proactive ourselves and making sure that

end users are communicating to those test kit manufactures. And also, not just about our needs, but also about how they can get the specimens that they need to do the testing, and try to make it as easy for them as possible because we know we're -- this field is not where their money comes from.

DR. FISHMAN: Dr. Strong.

DR. STRONG: Mike Strong, I'm still retired. Since I've been through this process before myself I can comment on it. When that testing first came out, of course, we were doing this for the blood industry and it was a nationwide clinical trial probably the first time that's ever happened in a test kit environment. And there were several blood centers that also were involved with tissue recovery. Ours was one of those. And the thing that worked for us to get the two NAT TMA manufactures to cooperate for tissue was to ride on the coat tails, as you say, of the blood testing. Because there's not enough samples to be, as she already spoke to, that it's not worth their while. There's just not enough

cases for them to put a lot a lot of money and to developing a test kit that's specific to tissue and cell donors.

But if there's partnerships that can be arranged with blood centers where the volumes are such that it's worth their while and it can be folded in to development of test kits that include this, that's where we were successful. So both with Gen Probe and Roche, we partnered with them to include tissue testing samples and there's where the partnership comes up for the tissue banks.

I know MTF has participated in studies because they have a large volume of samples. They have enough that they can select from. And many tissue banks actually have samples that they store for the lifetime of the tissues that are in stock. So there are samples available, but it's a requirement to do a partnership because it requires a collaboration between one of a high volume user like a blood center, the tissue center, and the test kit manufacture, and to some

extent the FDA. Because that requires some communication about how to best qualify these tests to meet the needs of the transplant community. So it's doable, but it requires a fair amount of coordination.

DR. FISHMAN: Other comments on this question? okay, last question. How can we access and utilize data that already exists in the HCTP field, such as that collected by testing establishments? There's an assumption underlying this particular question that there are data -- that there are such data. I have the advantage of not being in the field, so I can assume that this was written with knowledge of secret files. (laughter) But I don't know that to be a fact. We have no secrets in the organ world.

So how do we get more data? And I think also from the organ arena, transmission events in the organ arena are mandated and they're mandated for multiple different levels. So at the clinical center, at the OPO, other places that might have positives. So it doesn't always occur, for sure.

But it is a requirement of participating in the organ system. The question, are there such data and how do we get more access to them?

DR. MCCLURE: Well, I don't, I don't think that there's any secret knowledge that (laughter) the group had when coming up with these questions, but more so, you come to meetings like this and you always hear people presenting on some data that they have. And, you know, so there's a question of sometimes this is really great, very helpful information. Is there a way to -- as people are gathering this type of data that we can try to encourage, better encourage people to share this data somehow or publish this data so that, you know, maybe further the field will be able to pick up with additional studies on top of it. Or so that

we're not all doing the same studies, but, you know, progressing forward and learning as much as we can from the information that's out there.

DR. FISHMAN: Comments. I'm sorry. Yes, please.

DR. PELTIER: Yeah, Linda Peltier, McGill University. For cell therapy there's CIBMTRs collecting from every centers who are doing transplant who are fact certified to be giving the data and providing data. So there is a bunch of data, but it doesn't necessarily integrate, also, the kit you used to do all the testing. So maybe we can improve the collection data that different centers are doing and like a group CIBMTR and maybe use it from there on. And we can even go retrospective if we want to, and there's a way do it.

DR. FISHMAN: Dr. Eastlund.

DR. EASTLAND: Ted Eastlund, New Mexico, Minnesota, Wisconsin, retired. This question

about how can we access practical data from tissue that could be helpful, maybe in managing samples and then new testing or what's needed in the future. I thought of an example of that, but it doesn't come up an answer. But I worked for, almost a whole year, or a whole year, with a tissue bank and reviewed donor charts of 4,000 in a year. And I would come across some that I was told, the sample's hemodiluted. And I thought I knew everything, but again, one more thing I didn't really understand and figure this out. I thought I knew a lot about hemodilution. Well, I found out this is a common ordinary thing. And in that year I either had six or eight and I asked the lab to notify me. That they said it looks like watery blood. And they had, long before me, already done automatic things like hematocrits, doing total protein, and setting up a system that if it's a total protein that's high enough.

And let me explain what happened. Out of those, let's say eight; seven of those had basically, normal total protein. Now, you can

say, oh, they got plasma transfusion, but they didn't. And that was, to me, puzzling but it wasn't to them because they had set up a situation to solve the problem. And how can you get this watery blood with a good protein content? And I was left with the fact that, you know, when the body dies it settles out the blood and where the needle goes is important. Is it at the -- in the heart, in an area where a lot of red cells have settled out?

Well, normally when you want to do a hematocrit you mix up the tube. But you just can't lift up the body and mix that up. So is there another -- now, this is not a giant problem, I understand. And it's a hidden problem, not to the big tissue banks, but to a lot of the smaller ones, it is. Is there something practical you should be doing? Putting the needle in and pushing it in and out a few times? And so, it is an issue of collecting data that's already out there and then trying to solve the problem. Not necessary, regulatory wise, but solve it and share

the results and there could be many different examples like that. That if these problems were shared readily or if you sought the specific problems they're having maybe we'd all learn things and even regulate some things if needed.

DR. FISHMAN: I would make a comment in relation to that which I think is valuable. And the notion is, is that there are a lot of data, but there's not a lot of cross communication between communities. So data that are presented in one venue, not necessarily seen by anybody else, and it might be -- and I don't suspect it's the job of the FDA, but of the society's or the other groups, to collect these data and to assemble them in some from. And some of it may be online publication which is available now, but wasn't in the past. Some of it might be meetings that, like this, that basically bring together groups that have data from different arenas. And I think this happens too little, but somebody could do that.

And the other I would refer to is, Matt

mentioned Project Notify where at least there is a collection of transmission events so that you can look up and say did this every occur before or who often and what situation. But doesn't address the issue of which assay was used and what kind of patient population, for what kind of discussion.

DR. MCFARLAND: Well, I think we were thinking along similar lines because it occurred to me, is this fundamentally a question, at first, of a place to hold the data, a nonbiased party that can keep those data that can have for sake of a better word, a sandbox for people to ask questions about these data and come up with various sort of collaborative issues. And the question is, what would necessarily be the right thing? Would some place in HHS be the right place? I don't know. But is that sort of along the lines of what you were thinking because --

DR. FISHMAN: Yeah. I mean, it depends on the goal. So for example, just think of a concrete example. So in the organ transplant arena, we have an infectious disease community of

practice where, which is generally about management. It's not the saw an interesting case of, it's the I've got this case and I don't know what to do with it. But it serves that specific function. You could make these communities do whatever you want now and they're online, and the number of responses that you get is rather rapid -- that you get rapidly is quite, quite impressive.

So people are engaged because it's their life's work. So I think that is a question of finding the right home for those kinds of interactions. Oh, please.

MR. LOVERDI: Jason LoVerdi from AATB. Just to make everybody aware, we are collecting data from 2012 and 2015 in the National Tissue Recovery through Utilization Survey. This survey was actually conducted back in 2007, but it's been a while since this has been repeated. We do collect data from all aspects, from

(inaudible), disease testing, to

referrals, recovery, processing

storage, and distribution. And that should be done by the end of the year.

DR. MCCLURE: Can you comment on who will be filling out that survey?

MR. LOVERDI: So we expect, from our accredited banks, 100% participation as it is an accreditation requirement. We are asking that some recovery agencies that are not accredited participate. I can't speak as to whether they will participate or not. But all of our banks will absolutely participate.

DR. FISHMAN: Other comments? Hearing none, I think we're adjourned for today. Thank you all, and thanks again to all of our excellent speakers. (applause) Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing Please fix spacing

(Whereupon, the PROCEEDINGS were

adjourned)

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CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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