

NATIONAL INSTITUTES OF HEALTH

PUBLIC WORKSHOP:
EMERGING TICK-BORNE DISEASES & BLOOD SAFETY

Bethesda, Maryland
Thursday, April 6, 2017

PARTICIPANTS:

Welcome Address:

PETER W. MARKS, M.D., Ph.D.
Food and Drug Administration

**Announcements, Objectives, and FDA Perspectives
on Emerging Tick-Borne Diseases:**

DAVID A. LEIBY, Ph.D.
Food and Drug Administration

Plenary Presentation on Tick-Borne Diseases:

PETER J. KRAUSE, M.D.
Yale University

**SESSION 1: Biology, Epidemiology, and Clinical
Burden of HGA**

Anaplasma phagocytophilum, Etiologic Agent of
Human Granulocytic Anaplasmosis:

CARA CHERRY, DVM, MPH
Centers for Disease Control

Clinical Aspects of Human Granulocytic
Anaplasmosis:

J. STEPHEN DUMLER, M.D.
Uniformed Services University of the Health
Sciences

**SESSION 2: Biology, Epidemiology, and Clinical
Burden of Other Emerging Tick-Borne Diseases**

Other Emerging Tick-Borne Agents:

SAM R. TELFORD, III, Ph.D.
Tufts University

PARTICIPANTS (CONT'D):

One State's Perspective on Burgeoning Tick-Borne Diseases:

ALFRED DeMARIA, JR., M.D.
Massachusetts Department of Health

Roundtable Discussion I:

Morning Speakers:

BRYAN R. SPENCER, MPH
American Red Cross

HIRA L. NAKHASI, Ph.D.
Food and Drug Administration

SESSION 3: Transfusion Transmission

Transmission Risks Posed by Emergent Agents:

DAVID A. LEIBY, Ph.D.
Food and Drug Administration

Incidence of Transfusion Transmission (HGA and Other Agents):

SUSAN L. STRAMER, Ph.D.
American Red Cross

SESSION 4: Mitigation Efforts

Mitigating Infectious Risks of Blood Transfusion:

LOUIS M. KATZ, M.D.
America's Blood Centers

Conceptual Framework for Test Development:

RAYMOND P. GOODRICH, Ph.D.
Colorado State University

PARTICIPANTS (CONT'D):

Risk-Based Decision Making: The ABO Approach:

JUDIE LEACH BENNETT, LLM
Canadian Blood Services

Roundtable Discussion II:

CAPTAIN ROLAND L. FAHIE
Department of Defense

ROGER Y. DODD, Ph.D.
American Red Cross

JAY S. EPSTEIN, M.D.
Food and Drug Administration

Summary & Wrap-Up:

DAVID A. LEIBY, Ph.D.
Food and Drug Administration

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P R O C E E D I N G S

(8:30 a.m.)

DR. LEIBY:: Thank you and good morning. My name is David Leiby. I'm from FDA CBER and I am your moderator/host whatever you wish to call me, but more on that later. However, to begin, it is my distinct pleasure to introduce Dr. Peter Marks who is the center director at CBER and he'll provide you with some welcome comments and then address. AV is you could please put up the first talk, thank you.

DR. MARKS: First of all, good morning and thank you very much for attending today's workshop on emerging tick- borne diseases and blood safety. I want to start by taking this opportunity to thank FDA's partners in planning this workshop, AABB, America's Blood Centers, The National Heart Lung and Blood Institute, the National Institutes of Health, Department of Defense and the Department of Health and Human Services.

Having lived and practiced medicine in an area of Connecticut and Massachusetts for a fair amount of my life, I'm not too unfamiliar

with ticks on both a professional and personal basis. I've often had the opportunity to stare down at the adesia through the microscope in the hematology laboratory trying to distinguish it from malaria and have gotten the size difference right as well as the pigment differences. But also, have had to deal with its consequences in asplenic patients and in immunocompromised hosts and unfortunately have actually watched some tragedies due to the babesia as well. That's the professional involvement.

As somebody who's lived in those areas as well, particularly when we lived in a somewhat rural area of Connecticut, I can tell you I know the Ixodes tick up close and personal having picked it off of my entire family, my dog, my cat. Although it kind of just hangs on to the cat's fur and kind of falls off but they're very prevalent and it is something we have to deal with because of our local wildlife. And although the Ixodes Scapularis and the deer or black leg tick is perhaps best known for the vector for the agent of Lyme's Disease borrelia or doryphore, it's also the vector for a number of other tick-borne

diseases including borrelia miyamotoi, babesia microti and anaplasma thuyocytophilium, the cause of human granulocytic anaplasmosis which is the focus of one of today's sessions.

We probably should also not forget that although Ixodes is a frequent vector particularly in the Northeast where we have deer that cohabit with us in our salad bars known as our front yards. There are other species of ticks including dermacenter verabolis, the dog tick, which can transmit a variety of potentially life threatening infections including Rocky Mountain Spotted fever and tularemia and there are many others.

So, just as might one consider an unwitting host to various pathogens that it may carry as a result of a blood meal, collected units of blood conserve an analogous function. Today's discussions will focus on various aspects of tick-borne illness, ranging the biology, epidemiology and clinical aspects of tick-borne agents to the incidents of their transmission through transfusion and finally to strategies to mitigate their transfusion transmission. We

really hope that you'll find the program stimulating. I want to take one last moment and thank David and others from FDA who've worked hard to help organize this from our side and thank you again.

DR. LEIBY:: Thank you, Peter. It is certainly quite true that ticks seem to be finding their ways into our lives every day. Whether they're on us, perhaps our children, the pets that come back into our house, you never know where they're going to appear. So, I think it's very important that we talk about ticks today. This is just an opening presentation which I'm going to give some announcements about the day, state the objectives, provide a little bit of FDA perspective on emerging tick-borne diseases and then close with a little bit of levity so we're not so serious and I'll provide some thoughts of my own.

First of all, I need to do a lot of thank yous because this was a great effort by a number of people to put together this workshop that you're benefiting from today. This is listing of the individuals on a scientific program committee

who all contributed to developing the scientific program identifying speakers who were appropriate and then actually coming up with some of the questions which you'll see later for the round tables. In addition to myself, Cara Cherry from the CDC, Robert Duncan at FDA CBER and Etter at FDA CBER, Captain Roland Fahie from the DOD in the Armed Services Blood Program, Sunjay Kumar at FDA CBER, Dr. Lou Katz from Americas Blood Center, Babita Mahajan at FDA CBER, Susan Stramer from the Red Cross and lastly Shimian Zu here from NHL.

Probably most importantly are these three ladies, Pauline Coltrell, Kimberly Jones and Jennifer Scharpf from FDA CBER who did all the leg work behind the scenes. They're the ones who made arrangements or made sure the arrangements were made for the speakers to get here. They're the ones who printed all the materials that you received today, stuffed all the folders that you received, did all the behind the scenes leg work as well as putting out a few fires that inevitably come up. So, if you see them out at the tables, be sure to thank them because without them none of this would have gotten done.

Lastly, although Dr. Marks has already mentioned them, I want to mention them again, our sponsors because they were key. Without sponsors as well, we wouldn't have been able to move forward. First of all, AABB and Americas Blood Centers are the ones who are keeping you caffeinated this morning providing you coffee, tea, water, snacks later this morning at the break and this afternoon. So, please take your time to thank them. The Department of Defense was instrumental in providing funding for speakers. The Department of Health and Human Services helped us out with the transcripts that you'll be able to see online at some point. As Peter already said, the FDA and the leadership were important in supporting this concept to this workshop and also helping to bring in several speakers. Lastly, the National Heart Blood and Lung Institute here at NIH, were the ones that allowed us to get into Natcher Auditorium to make this a rather comfortable experience for all of us. So, when you see them, thank each and every one of them.

Now as far as workshop logistics, we're

going to have four sessions today as you can see in your agenda with a variety of speakers and we'll have five minutes of questions or longer depending on how things flow after the speakers speak. So, please use the microphones and identify yourself when you ask the questions in order that the person keeping the transcripts can follow along. There will be a morning and afternoon panel discussion made up of the speakers and a couple of others which are added. In these panel discussions, we'll answer questions that were actually provided to them ahead of time so at least we'll have some thought and perhaps some discussion and some exchange, we'll see how that goes.

As I mentioned earlier, we have a morning and an afternoon break. Those breaks are a half hour long because I know if I made it for 15 minutes, no one would come back in that time. At least a half hour gives you enough time to exchange information to one another because I know this is an important time to meet colleagues and to discuss issues both tick issues as well as other issues.

As far as lunch, you have your choice of cafeterias on the NIH campus. Probably the easiest one is in the next building over, out the door here and to the left, up the steps and across the foyer. I believe they've been alerted that there's a large group here and they should be prepared but I can't vouch for that. Restrooms are out the doors to the left and the right, you'll find them.

Meeting transcripts as I suggested, will be post at a later date on the FDA site but the slides will not be posted. I think you have many of the slide presentations in your handouts today. Lastly, there will be a summary publication, at least it is anticipated and I've been charged with writing it or seeing that it gets done, so I'm quite certain by the end of the year you'll see the summary publication.

Now, talking a little bit about workshop objectives, first of all we'll discuss tick-borne pathogens that continue to emerge as threats to blood safety, the effectiveness of current and potential mitigation strategies and the general approach to decision making on blood

safety interventions. In putting together this workshop, the Committee had several objectives and design elements. First of all, this workshop is designed to be forward thinking and horizon scanning. We're trying to think about what comes next, what issues that we might need to deal with in the future. So, what we're talking about is perhaps in some cases, not everything that is here now but something that we do anticipate in the future.

It's also designed to be informational so, hopefully you'll go home today with a lot of new knowledge about tick-borne diseases and concerns even if you don't live in the Northeast. And the key element of this is not designed to be policy driven. So, we're not making any decisions today, the FDA is not issuing policy, it's just informational and discussion point. And perhaps most important, we wish to enlist the leaders in the field and I think we have them here. It's a small group so in some respects it's not difficult but they are the ones who are driving tick-borne diseases and their investigation and study and I think you'll be rewarded by some very

fine presentations.

Lastly, just to head off any discussions or questions, we're going to focus on emerging tick-borne diseases and agents. So, they'll be limited discussion of both Lyme Disease and Babesiosis. Lyme has been around for decades. There are hundreds of thousands of cases each year, so Lyme is actually, in some sense, been well characterized but clearly there are issues with Lyme. We could spend days in a workshop on just Lyme. Another fact is that despite all the Lyme Disease cases, to my knowledge there has never been a reported case of transfusion transmitted Lyme. So, for today, we'll leave Lyme out or as a backline player. As far as Babesiosis, there has been a workshop on Babesiosis. There have been several B PAC's son Babesiosis and there are also IND investigational studies underway at this point of Babesiosis so it seemed appropriate that that agent was covered and we had focused on emerging agents only.

The topics for discussion and Peter eluded to some of these, we're going to discuss the biology, epidemiology and clinical burden of

anaplasma phagocytophilum and other emerging tick-borne disease, some perhaps you're not even aware of. We'll talk briefly about the performance characteristics of currently available diagnostic assays for agents of concern and we'll talk about known potential risks of transfusion and transmission posts by emerging tick-borne agents. We'll also have some discussion on current and potential mitigation strategies, what those might be. Lastly, towards the end of the day, we'll have some considerations in the decision making process for safety interventions because that's always a popular topic.

Now one final thought, and this comes from me as a personal thought and I don't represent FDA in this thought, but I thought I was worthwhile to at least think about arboviral agents and diseases versus tick-borne diseases. Arboviral agents are ones that we are constantly confronted with. They are an ongoing issue and one that we've addressed in blood safety many times. And tick-borne agents, the subject for today is rather different. And so, when I

thought about this, I tried to come up with an analogy of arboviruses and tick-borne agents. What it shows is it went to Aesop's Fables. And I not surprisingly, perhaps maybe I went with the tortoise and the hare and I love this illustration. It's from a 19th century illustration by LaFontaine's Fables by Gene Granville. What I'd like to propose today is that the hare represents arboviruses and the tortoise represents tick-borne diseases. In fact, if you put two more arms and two more legs on a tortoise he would look like a tick anyway.

Arboviral diseases, you're all familiar with these. In many cases, they appear with little prior warning. They frequently move very rapidly through a naïve population, potentially causing endemics and we've seen that. In some cases, in the absence of reservoirs or other factors, they often burn out or in the case of the hare, they tire quickly. We've seen many U.S. examples, some of which apply to this and some that do not. Now probably the first one is West Nile Virus which arrived in the United States in 1999, quickly moved across the U.S. but

established reservoir population in birds. To this day, we still test for West Nile Virus and it's still a major issue for us.

Dengue Virus, we see fewer cases. We had some concern about dengue virus and certainly with different sero types it has different issues that may pose problems for us in the future. Chikungunya virus although we've seen some sporadic cases, I think the numbers have declined as I checked it the CDC. Of course, Zika Virus is the top of the day in many areas, we just don't know about Zika Virus. There is too little known. CDC just came out with a new publication this week learning more about the effects in unborn children and in infants. It was also the factor of sexual transmission, this is something that we're not going to be to understand for a number of years.

Lastly, Yellow Fever Virus has become very noteworthy lately because we see it in Brazil. We see monkey populations dying who are susceptible but at this point, it is largely a sylvatic cycle hasn't spilled over into the urban cycle so it's worth watching. So, those are the

arboviruses.

I want to contrast those with our subject today which is tick-borne diseases. In many cases, tick-borne diseases emerged gradually and they expand their geographic ranges rather slowly or I like to say they're plotting. I'd like to use a quote and Sam, you'll perhaps not be surprised but from Sam Telford's mentor at Harvard, Andy Spielman used this quote and I've used this numerous times and I still love it. Lyme moves on the wings of birds and Babesia on the backs of mice. Now Lyme Disease and Sam can correct me later if I'm wrong. Because of the life cycle and the way, it passes transtately in through some of the different stages that a tick can be moved or transmitted more rapidly through birds. That's why Lyme Disease spreads much more rapidly compared to Babesiosis. Babesia however, doesn't have that advantage of birds so it's dependent upon those white footed mice that we saw in some pictures early from Dr. Marks and they just don't move as fast. So, it's establishment in its reservoir and its population has expanded much more slowly.

Now many tick-borne diseases have reservoir hosts and they persist over time. There are certainly U.S. Examples. Lyme Disease, as I said, has been around since the early 80's or the 70's, first discovered in Old Lyme, Connecticut and we have tens of thousands of cases every year. Babesiosis is a major problem as far as a public health issue in this country. We're going to talk today about human granulocytic and monocytic ehrlichiosis and we'll also hear, I believe, from Dr. Krause about relapsing fever *Borrelia miyamotoi*, perhaps actually I'll learn how to say that today. But what I'd like to leave you with is the moral of the story is while slow and steady tick-borne diseases are worth watching and that's the topic for today. I'll leave you with this last slide and this is close to home by John McPherson. Of course, you can all read it, it's Noah's ark, he said wait for the ticks, we forgot the ticks. Thank you.

It is my privilege and honor to introduce our speaker today and that is Dr. Peter Krause. He's a research scientist at the

Department of Epidemiologic and Public Health at Yale School of Public Health and the Yale School of Medicine in New Haven, Connecticut. He received his BA with honors in biology from Williams College and his M.D. from Tufts University School of Medicine. He completed his pediatric internship and residency at Yale New Haven Hospital and Stanford University Medical Center and his pediatric infectious diseases training at the University of California, Los Angeles, UCLA. He joined the faculty at the University of Connecticut in 1979 and moved to Yale in 2008. I've had the pleasure of knowing Peter for many years and hearing his talks and I'm sure you'll be rewarded as well today.

DR. KRAUSE: Thanks very much Dave and certainly I thank you and the organizing committee for inviting me here to speak, it's certainly an honor to be here. I will say that I will probably violate that last dictum by David. It's too tempting to talk about Lyme Disease and Babesiosis as an example of certain principles that one wants to talk about so please forgive me for that. But the main focus of the talk

certainly is not on either of those organisms.

So, the title of my talk is Emerging Tick-borne Disease, Diseases in Blood Safety, Present, Past and Future. And the outline of the talk as shown here, I'm going to first talk about present tick-borne and tick transfusion borne, TT-B infections in the United States. The point here is that there are many tick-borne infections but only a few are transmitted through blood transfusion as well. And then we'll talk about past experience with tick and transfusion borne infections and lessons we've learned and I've chosen five. Firstly, the pathogenesis of tick-borne microbes helps to determine blood transfusion transmission. The geographic range and incidence of tick born and tick transfusion pathogens are increasing. The discovery of tick and transfusion borne infections takes time. The control of tick-borne and tick transfusion borne infections is difficult and successful discovery and control require a team effort. Then I'm going to talk about future imperatives including the need to accelerate the discovery of new tick and transfusion borne pathogens to

better define the scope of the threat once a pathogen is identified and when you can do that through surveillance and modeling and certainly being away of geographic variability. So, what's true in one area may not be true in another. And certainly, improving control of tick-borne and transfusion borne infections is a central goal for future work.

So, I'm going to list here three tick-borne agents that we find in the United States. The number of tick-borne agents worldwide is much greater than what I'm showing here but these are the ones we're concerned with in this country. And, of course, Lyme's Disease heads the list in terms of approximate number of cases per year with about 30,000 cases. Babesiosis and human granulocytic anaplasmosis are relatively similar, about 2000 cases a year. Tick-borne encephalitis plus deer tick virus about ten year. And then two newer agents, so they're six all together transmitted by each of these hard body ticks, Ehrlichia mirrors like infection and Borrelia Miyamotoi infection and these are not yet nationally reportable, more

recently discovered and again not nationally reportable at present.

And then there is a slew of agents transmitted by *Amblyomma* *dermacentron* and *Ornithodoros* ticks and I've listed them here. And at the top of the list in terms of number of cases reported is Rocky Mountain Spotted Fever and this is variable over time but currently about 2000 cases a year. Human monocytic ehrlichiosis 900 cases a year tularemia 300, soft tick relapsing fever, *Borrelia recurrentis* and *parkeri* about 25 cases a year. Colorado Tick Fever 10, *Ehrlichia ewingii* less than 10 and then a number that are not nationally reportable such as southern tick associated rash, *Rickettsia parkeri*, *Rickettsiosis* and 346D *Rickettsiosis* which we'll probably hear further about from Steve Dumler and other. And then Heartland virus and then finally *Bartonella* species which I put in italics because it's not clear or it has not been definitively demonstrated that this is transmitted by ticks although the organism is found in ticks. But that's not fully certain at the present time.

So, then if we look at tick-borne agents that are transmitted by blood transfusion it's a subset of the ones I've just discussed. I've listed them according to the number of transfusion cases that have been described to date with Babesiosis that is *Babesia microti* greater than 200 cases found in the East and Mid-Western United States. HGA about ten cases a year, East and Mid-West. Babesiosis due to *Babesia duncani* which is a species found in the West Coast, three cases, tick-borne encephalitis two, soft tick relapsing fever and this would be primarily *Borrelia recurrentis* two, Rocky Mountain Spotted Fever and Colorado Tick Fever one and human monocytic ehrlichiosis has been transmitted through renal transplantation. An organ donor transplantation, presumably the blood in those donor organs is how the organism is then transmitted. So, this is a list of somewhat limited in terms of the numbers and the actual number of cases undoubtedly much greater than what is shown here. So, one might say three cases all together or it's one, two or three, how important is it. But the actual number of cases,

again, are undoubtedly much greater than what we see here.

So, I'd like to now talk about some of the principles or lessons that we've learned from studying these tick-borne diseases in the past. Firstly, the pathogenesis of tick-borne microbes helps determine blood transfusion transmission. I wanted to compare babesia microti with borelia burgdorferi to gain some insight. So, Babesiosis I think most of you know is caused by a protozoan parasite and the family Apicomplexa. Target tissues are erythrocytes. Transmissions are through each of these ticks, blood transfusion and transplacental transmission. Clinical presentation is a malaria-like illness that can be quite severe, in fact, fatal in immunocompromised patients and actually those who acquire the infection through transfusion, the diagnosis is made on epidemiologic grounds, that is a person who has lived in or traveled through an endemic area or received a blood transfusion within the previous six months or so. Typical symptoms, microscopy, PCR and antibody. Treatment is atovaquone, azithromycin or

clindamycin and quinine.

So, here is a slide, a thin smear from a patient with Babesiosis. This patient was relatively heavily infected. These are the red cells as you are all aware and here are the babesia within those red cells. This patient had about a 10 percent parasitemia, quite high. It can in fact, go up to 80 percent but that would be rare. Most patients have a one to three percent parasitemia but that may not seem like a lot but if you think about it, it's millions of red cells that are infected. So, there's really a heavy infestation for most cases of Babesiosis in the blood.

The other problem with Babesiosis is there's a persistence of the organism is at least is measured by PCR looking at amplified DNA through PCR and these show two studies that were done that have been done demonstrating the long duration of parasitemia following infection. The first is a study that we did looking at patients who had Babesiosis. There was a non-treatment and a treatment group. This study was done at a time when the only treatment was

Clindamycin and quinine which has a lot of side effects. In those days, one just followed these patients and most of them would resolve without therapy. So, what we did is to enroll patients who had Babesiosis either treated or untreated. That is the treated patients would be the more severe cases and we followed them every three months doing PCR. And this is a Kaplan-Meier Plot showing the decreasing number, PCR positivity in these patient groups are about 25 in each group. These patients were symptomatic in the first week or two and then all of this from here to here basically symptomatic. And you can see in the non-treatment group, we had patients who went out, we had one patient who went out 27 months before clearing. That patient actually recrudesced, stopped getting tested at 18 months and then came in about 9 months later in the early Spring before the tick season with a very severe case of Babesiosis. So, we thought that was recrudescence.

These patients, the non-treatment patients were picked up through our sero survey on Block Island where we would just do testing for

Babesia, PCR testing and found positive individuals who were asymptomatic. Very similar to the blood donor group here shown in this graph and this is by Mortiz et al, a recent paper in the New England Journal, looking at the duration of PCR positivity in two groups, those that were antibody negative and positive. You can see the antibody positive group went out interestingly about 27, 28 months. So, the organism can persist in the bloodstream for quite a while. That is obviously important in terms of transfusion, transmission.

Lyme Disease in contrast is not in the blood or not in the blood for very long. The cause of the pathogen is burgdorferi. It targets six tissues, skin, joints, heart, CNS. The transmission is by each of these ticks. Clinical presentation is erythema migrans in about 90 percent of patients and viral like symptoms in about 10 percent. People with erythema migrans, some do have viral like symptoms as well. The diagnosis again is epidemiologic but also symptoms. Antibody, PCR and culture and the most important diagnostic approach is identifying a

person with an EM rash. Treatment is Doxycycline, Amoxicillin, or Ceftriaxone.

So, here's a patient who, this is a picture long ago of erythema migrans. This is before therapy was discovered. People didn't know how to treat this initially. This patient was bitten here. The organism started to proliferate and moved outward and you could culture any of this area and you'd get organisms. This is a non-disseminated case and this is a case where there's been dissemination. So, the organism has entered the bloodstream and the initial bite was here but now you see additional lesions because of that bloodborne dissemination.

So, if we compare Babesia and Lyme, it becomes apparent why we see cases of transfusion, transmission with Babesia and not with Lyme. The primary target tissue for Babesia are erythrocytes whereas with *Borrelia burgdorferi* it's fixed tissue. Both invade the blood but the concentration in blood is moderate to high with Babesia whereas low with *Borrelia burgdorferi*. The duration of bloodstream is months to as long

as two year babesia and probably no one has well defined this but probably hours for borelia burgdorferi. And therefore, we see transfusion, transmitted cases of babesia, not Lyme.

So, a second lesson that we've learned is a geographic range and incidence of tick-borne and tick transfusion borne pathogens are increasing especially those transmitted by *Ixodes scapularis*. The Lyme Disease was first reported here in Southeastern Connecticut in Old Lyme which is just east of the Connecticut River and actually preceding that, the first definitive case of Babesiosis in the United States was reported on Nantucket Island, it was the third case overall. The first was reported in Yugoslavia and the second in California all though, I think the species in either was well defined. This was shown to microti on Nantucket Island. These organisms have moved northward and westward and southward over time.

Now this slide shows Lyme Disease and Babesiosis cases in Connecticut and how they've advanced geographically over time. And so, we charge here the time when towns, these are all

towns here, became endemic and as defined by two consecutive years of reporting of the disease. In red, you see what the state of endemicity was in 1991 and remember Lyme Disease was reported in the early 70's so by 1991, much of the State, all though not all of the State was endemic. But there were a few areas that were not endemic. Babesia also started in the Southeast portion of the State, was first noted there, and it moved also westward and northward but more slowly. So, by 2008, you see these new areas that had now and virtually the entire State of Connecticut was endemic for Lyme but still there were a number of areas where Babesiosis was not endemic. So, it moved more slowly than Lyme did. Perhaps, on the wings of birds, the backs of mice help explain this but Sam can probably give us better information about that.

I wanted to just point out that, I'm going to show you a national slide next. But you'll note that in 1991, not all of Connecticut was endemic. There were areas, the green and the light orange were not endemic at time, were not reported at those states. But in this slide, we

see the advance of Lyme Disease on a national scale. This shows the entire State of Connecticut is endemic from 1993 through 1997. In 1991, we know there were towns that were not endemic. In any event, the point I'm trying to make is as you look at this, you see spread from 1993 to 1997 to 2008, 2012 and there's tremendous spread of this disease over time. And in the Mid-West, the same thing. You have the spread of the disease from 1993-2012. But not only was there sort of expansion geographically but in those areas that were called endemic, there was actually expansion within these sort of throwing out the endemic areas in those areas.

I just wanted to show this slide to just demonstrate that these diseases are tick transmitted diseases, many of them are worldwide in distribution. So, for both Babesia and Lyme and HGA, you find cases in this temperate zone throughout the world. And along with the geographic expansion came an increase in a number of cases from 1982 to 2012 shown here and you can see that there's been certainly a steady increase in cases somewhat plateaued here. But the actual

number of cases estimated based on several studies to be about ten times the number of reported cases. The same increase in cases as shown here for anaplasma and the same for Babesiosis. I think one can safely say or it's very likely that for HGA and Babesiosis the actual number of cases is far greater than the reported cases, especially because both of these diseases are more difficult to diagnose than Lyme Disease which because of the EM rash, making like relatively easy in terms of diagnosis.

I show this slide of Rocky Mountain Spotted Fever just as a contrast to those Ixodes transmitted diseases. So, here we see there is an up and down incidence that one sees between 1920 and 2005 currently there's been a sharp increase in the number of cases. We don't know if the same will happen with Babesiosis, Lyme Disease and the other tick transmitted Ixodes, transmitted agents but right now we see as an increase. We'll see what happens over time.

And along with the increase in cases through tick transmission, we also see an increase in a number of cases through blood

transfusion. This is a study by Herwald et al and they identified all identifiable cases from 1979 through 2009. You can see here, there was a steady rise in the number of cases, most occurring in endemic states as shown by the light green but also in non endemic states because babesia infected blood can be transported from areas of endemicity to states where the disease is non endemic and cause disease there. Or people living in a non endemic area can vacation in an endemic area, pick up the infection, come back to their home state which is not endemic. If they have asymptomatic disease they may then donate blood and transmit the disease in that way.

Lesson 3, the discovery of tick transfusion borne infections takes time. What I've listed here are the diseases transmitted by ticks and blood transfusion. The years from the first case to the first transfusion case. So, for example, with HGA was the first human case reported in 1994, the first transfusion case in 1995. So, we have a five year disparity between the first human case reported and transfusion case, six years for HME, for Babesiosis 21 years,

for Rocky Mountain Spotted Fever, 83 years. The numbers aren't terribly important. Well, I think, they're important in two ways. It does take a while before -- we don't see cases reported in humans and then immediately we'll see a blood transfusion case and it's simply because transfusion transmitted cases are fewer in number and require further investigation to identify.

The other thing I'll point out though is if you look at the year in which these diseases were discovered and this disparity between first human case and transfusion case, they're smaller as one becomes more current. That is, it seems like we're getting better at identifying transfusion transmitted cases as time goes on. I think there's a greater awareness, a greater appreciation of the importance of this and we have better tools to discover transfusion transmitted cases.

Lesson 4, control of tick-borne and tick transfusion borne infections is difficult and I'm going to use Babesiosis as an example. So, the pathogen was discovered by Victor Babes, a Romanian, although some would say Hungarian,

others would say European pathologist. He discovered Babesia as a pathogen in Romanian cattle in 1888. The first human case was not described until 1957 by Skrabalo et al and that was in Yugoslavia. Then, in 1970, Western described the first human case in the United States on Nantucket. In 1979, Jacoby described the first transfusion transmitted case of Babesiosis. The 1990's was the beginning of the emergence of these diseases really started to pick up in terms of number of this disease and then the use of history of Babesiosis for blood donor screening. So, one approach, of course, is when you are collecting blood from donors, you ask if they ever had Babesiosis and if they say yes, you do not allow them to donate. That began in the 1990's and that's undoubtedly prevented a number of cases. But as an overall strategy, of course, it's not been successful enough because we've seen this rise in the number of transfusion cases. In the first use of laboratory screening of donor blood was in 2012. It's a fair amount of time, 1979 to 2012 before we were able to start with potentially and probable effective measures for

prevention of transfusion transmitted Babesiosis. I think that hopefully in the future it can proceed more rapidly. In defense of what's happened, it didn't really become endemic or really highly visible until the 90's. It's a complex thing, obviously, to develop a policy to prevent blood transfusions. So, it's not something one can do in a day, or a week or a year or even maybe a few years.

Finally, the discovery and control requires a team effort. This includes academics of blood transfusion services personnel, entomologists, federal CDC and State health departments, industry, NIH, primary care physicians and private foundations. Now, there's some glaring omissions here and I apologize, FDA obviously should be here, The Department of Defense and other federal organizations. But it takes many people and many disciplines to ultimately develop effective discovery and control measures.

So, future imperatives. Accelerating the discovery of new tick transfusion borne pathogens is certainly very important. And this

can involve field studies in ticks and in humans. A search for etiology of adverse transfusion events using new laboratory methods and old laboratory methods as well. Targeted studies of tick-borne pathogens are potential tick and transfusion borne pathogens. Once a pathogen is discovered to be transfusion transmitted, we need to know what kind of threat it is. Is it a small threat or great threat and we need to ask the question of how frequent is this event occurring and how severe is the disease that results that is the health burden. We can do this through surveillance and modeling and it's important that we are cognizant of geographic variability. And then finally, improving control of these infections is the third category that I'll talk about.

So, let's start with field studies in ticks and in humans and I'm going to use borrelia miyamotoi relatively recently discovered borrelia, relapsing fever borrelia as instructive in talking about this. So, borrelia miyamotoi thumbnail sketch the cause of the pathogen are borrelia miyamotoi which is a

relapsing fever borrelia group, target tissue or blood and fixed tissue, central nervous system cases have been described. Transmissions by Ixodes ticks possibly transfusion, possibly perinatal but we do not know that at this time.

The epidemiology, this disease will probably be found wherever Lyme Disease is found and cases, so far, have been described from Massachusetts, New Jersey, New York, Rhode Island, Germany, Japan, Netherlands and Russia. Clinical presentation is a febrile illness, a viral like illness lasting several days, sometimes followed a week or two later with relapse. And relapse is if you look at for miyamotoi there have been, I think the maximum has been three relapses. If you look at other relapsing fevers transmitted by soft ticks like borrelia recurrent risk there have been as many as ten relapses over the course of an entire year. But relapse is seen. I will say in the case studies that have been reported to date, actually only a minority of patients have had relapsing fever. That is relapsed their fever. They have an initial illness but many of these patients or

most of them have been treated relatively quickly. So, in other words, the lack of relapse that we see with miyamotoi may be more a sociologic phenomenon, that is these patients are seen and treated early and then a biologic phenomenon. So, if you took a patient, decided not to treat him which you wouldn't do, they might have a number of relapses. But relapsing fever has been seen with this agent in these clinical case series. Diagnosis is again, epidemiology. Does a person live or travel in an area where miyamotoi is found.

Symptoms we've talked about somewhat non-specific so you really need to make the diagnosis, you really need to visualize the organism on blood smear or in central nervous system if there is meningitis. PCR and antibody are also very useful. The organism can be cultured and small animal inoculation will also identify the organism but these are generally research labs that do that. Treatment is the same as Lyme Disease. Doxycycline, Amoxicillin and Ceftriaxone is quite effective.

The discovery of the organism is

interesting. It was first discovered in 1995 in Japan, named after a world famous entomologist, Dr. Miyamoto and this is a quote from an editorial that accompanied the first large case series in the United States, Molloy et al. Among other things, they commented about that case series which is quite excellent but they also made this statement. *Borrelia miyamotoi* infection was identified by reversing a traditional approach to disease discovery such as Lyme Disease, for example. First, identifying an infectious agent in a known vector than searching for human disease. This reverse strategy will no doubt become a model for future discovery of novel and infectious diseases. So, certainly our entomologist colleagues are going to be, I think, very important in the future in discovery of new tick-borne transmitted agents and ultimately tick and transfusion borne agents.

The etiology of adverse transfusion events is another way in which we can discover tick and transfusion transmitted agents using both new and old lab methods including microscopy, histology, culture, small animal

inoculation, antibody testing and more recent methods such as PCR, multiplex PCR, high throughput genetic sequencing. We can also do targeted studies of tick-borne pathogens as potential tick and transfusion borne pathogens. That is, once an agent has been described as being transmitted by ticks, we can then look at the pathogenesis characteristics of that agent and decide how urgent it is, well there's always some urgency but some more than others. So, pathogens achieving high concentrations in the blood for a long duration that survive blood banking storage conditions are obviously ones that we'd want to focus on.

So, if we look at list of agents that are not yet reported to be transmitted through blood, but might be potential agents transmitted through transfusion, borrelia miyamotoi will probably top the list because it has a high titer in the bloodstream and has a long duration in the bloodstream. It is a cousin of Lyme Disease but it's different because the relapsing fever borrelia spend most of their time in the bloodstream and the relapses occur because the

organism can change its protein code so the initial immune onslaught that eliminates more of the organisms than becomes non-effective as the organism changes its code and then starts to multiply again. So, they spend most of their time in the blood whereas the Lyme agents basically are in fixed tissue as I mentioned.

If we look at Tularemia, it definitely can get high titer in the bloodstream but at least the data today would suggest that it's not there very long. It's very transiently in the bloodstream. And many or maybe most pathogens will have a blood phase but in many instances that blood phase will be very brief. A number of these may not be able to survive blood banking conditions because they are not, for example, like babesia inside a red cell. They don't find a cell to get inside and protect them. So, these agents we don't really know if they have high titer or how long the duration is, for Lyme Disease the answer is no. So, if we look at this list, the obvious candidate to look at would borrelia miyamotoi.

So, with Theresa Hendrickson and myself

and a few others, we asked the question whether transfusion transmission could occur in an animal model. We took ticks that were infected with borrelia miyamotoi and infected SCID mice. And then we took blood from these SCID mice and injected interperitoneally actually with plasma from infected mice. The blood was collected for a transfusion from an infected SCID donor mice once the parasite level was near 1 percent. And then we took the blood from these infected mice and these were then given to other SCID mice, C57 Black or DBA mice which are less immunocompromised and we transfused them with either fresh blood or blood that had been stored under blood banking conditions for a week. And then ultimately we looked at the mice that had received this blood and we did blood smears and spirochete motility to determine whether transmission had occurred. And this shows some spirochetes, some miyamotoi in the blood, in fresh blood and then here in stored blood. So, even after storage for a week, these organisms were still present and viable. After transfusion into an immunocompetent mouse, that

is a relatively immunocompetent, DBA's or C57 Blacks, we actually did see some spirochetemia although it was not very high. Whereas, even 28 days after transfusion in the SCID mice with stored blood, we found spirochetemia. And this just shows that we had three SCID mice here, this shows spirochetes in the concentration in the blood in the day's post transfusion. So, the SCID mice achieved a much higher concentration than the immunocompetent mice. One mouse wasn't infected but another had a slight limp as you see.

Now there is a very nice study by Thorp and Tonnetti that extended our findings. They did transfusion experiments in mice and found that not only red cells but also platelets could transmit platelet packs could transmit through blood transfusion. They also spiked human blood in blood banking conditions with borrelia miyamotoi, different components, red cells, plasma and platelets. And they saw whether the organisms would survive in blood banking conditions. These are leukoreduced and non-leukoreduced and you can see two different concentrations. There was transmission,

certainly with red cells and with platelets. It lasted longer with red cells, that is the survivability versus platelets. Plasma, the organisms did not persist in blood under blood banking conditions in plasma. These were the concentrations used in their mouse experiments. So, it does appear that, I mean, these two studies suggest that *borrelia miyamotoi* may be our next problem in terms of transfusion transmission.

So, that brings us to the next step which would be, we have a potential organism that could be transfusion transmitted but the next question is what's the health burden of this organism. What is its disease frequency and its disease severity. If it is relatively infrequent and it doesn't cause very severe disease, even if it is transmitted through blood it's not going to be a major concern. It still would be a concern but not a major concern whereas if the opposite is true then it would be of much greater concern.

So, *babesia microti* again, we see that the frequency, it's the number one transfused pathogen in the United States. Modeling shows

the infection will increase and continue to spread so it's frequent and its severity is great. The mortality rate among people who acquire the disease through transfusion has been variably reported but at least the Herwaldt study, I think it was 18 percent, some have reported as much as 21 percent so, that's a real concern. Miyamotoi, on the other hand, how frequent is that. We don't have a very good understanding of that at the present time but we've done a few sero prevalent studies and that the sero prevalence of miyamotoi is similar to that of microti. There have been tick studies that show that there also can be comparable and its variable. In some regions, you have less miyamotoi than microti but in several regions such as out west the miyamotoi infection rate in ticks is similar to that in Lyme Disease.

The severity of miyamotoi that I mentioned relapsing fever in anywhere from 1 to 10 percent of patients. Meningoencephalitis has now been reported in three patients. These were elderly individuals here were immunocompromised. So, the health burden of miyamotoi is not clear

yet. It may not achieve that of microti in terms of transfusion transmission concern but this remains to be seen.

So, finally I'd like to talk about the control of tick and transfusion borne infections. There's ecological measures, human protective measures and transfusion services measures, that is donor screening and pathogen inactivation. Integrated tick management tools are shown here. Personal protective measures such as wearing long sleeved shirts and long pants. Tick bite prophylaxis, giving antibiotics after you've had a tick bite, that's been shown to be effective. Doxycycline for Lyme Disease but not the other agents. Landscape modifications such as building a barrier if your house adjoins woods you build a barrier with wood chips or with stone. Ticks don't like to cross this, that's another approach. Chemical control, synthetic insecticides or natural compounds sprayed on property can be effective. Host targeted acaricides that would be in human, deer and mouse. With humans, you can put Deet on your skin or you can put permethrin on your clothing and that helps

prevent tick bites. There are devices to place acaricides on deer and mice. For deer, there's a four poster device which is effective but has a number of drawbacks and is not in wide use but there are areas that use this. And little mouse houses where acaricide is applied as they go in to eat some peanut butter has been used. Sam can give us a better rundown again on that but that, I think, has had limited success or not proven to be highly effective to date. I think Sam will probably be talking about host reduction or exclusion of deer and that has been shown to be effective in certain areas.

Host targeted vaccines, the only vaccine that has been used to date has been for Lyme Disease and that's no longer on the market. Finally, education and behavioral changes, very important to let people know about the biology and how to avoid ticks in the first place.

Finally, in a very nice review study by Bihl et al, strategies to reduce risk of transfusion transmitted infection. First of all, donor eligibility. So, you can ask the question, have you ever had Babesiosis. If the

answer is yes those folks are not allowed to give blood. Although, of course, we don't know if the persistence of the organism is life long and it probably is not but at least if you omit people who have had Babesiosis, you will decrease the risk for transfusion transmission. Processing in quality control to make sure there's not infection introduced at that step is probably not so important for tick transmitted agents but is for others. Screening tests, antibody, PCR are certainly an approach that can decrease transmission through blood. Storage of the pathogen and pathogen activation are another potentially very effective step.

The indication for transfusion, simply trying to limit the number of transfusions will decrease the number of transfusion transmitted infections. And finally, traceability in hemovigilance systems where you follow up on patients who've had adverse events from a febrile illness following a tick transfusion.

So, that's it. I did want to thank my funding sources. CDC, Gordon Llura Gund Foundation and the NIH. There are many, many

people who have helped me over the years and I'm very grateful to them. I, unfortunately don't have time to mention them all individually but this is a list. Finally, I'll end with this slide of Block Island where I've done research over the past 25 years. It's really been enjoyable.

I'll give one final funny anecdote. Andy Spelman was the one who was invited out to the island, Andy and Sam and they're entomologists, I'm a physician so, we worked as a team. and one time leaving the island, maybe the second or third time we'd been out there, I just remarked to Andy, what a beautiful, natural setting Black Island was. And Andy's comment was, Black Island is about as natural as tarmac. That's because the hand of man has been heavy on Black Island. Truly if man were not there, this would be old growth forest but it is shrub pretty much. Anyway, thank you so much and any questions, thank you.

DR. KUMAR: So, chronicity of anaplasmosis can you tell us anything about.

DR. KRAUSE: Chronicity of anaplasmosis, wow. I am unaware that there is sort of long term problems with that organism.

Again, with babesia we know that's the case or at least we know that immunocompromised patients can be infected for a long time and suffer symptoms. But I'm not sure about HGA and Steve would probably be able to answer that question better than I.

DR. KUMAR: Okay thank you.

DR. KRAUSE: I mean, there's two parts to that question, Sanjay, when I think about it. One is, are their long term symptoms but the other is does the organism remain in blood for extended periods of time. Again, Steve do you want answer at this point, maybe not. Steve or others will probably answer that question.

DR. DUNCAN: Hello. I'm Robert Duncan from the FDA CBER and I have a whole series of questions I'm going to try to boil down to one that you could answer. And that has to do with, you've told us many stories about the epidemiological spread of various agents, geographically and over time. The question that occurs to me is why. You've told us a lot but you've never said why and I'm sure that's a hard question to answer. And I also want to emphasize the reason why I have that

question is to try to project, where's it going to happen next. When is a babesia going to jump to another state. How long will it take and what are the factors that are restricting the further spread of these tick-borne diseases.

DR. KRAUSE: Yes so that's an excellent question actually Sanjay's is as well. Excellent question and I would be stealing Sam's thunder if I were to talk about that and I wouldn't be able to talk about it as effectively so if you'll hang around for Sam Telford's talk, I think he's going to explain that is that true Sam? Yes, okay. He'll just give you the story from the beginning and it's quite fascinating actually. Any others? All right, thank you again.

DR. LEIBY:: Thank you, Peter. The next presentation is entitled Anaplasma Phagocytophilum Etiologic Agent of Human Granulocytic Anaplasmosis and it was to be presented by Dr. Cara Cherry of the CDC. Unfortunately, I was on the phone multiple times with Cara yesterday from the Atlanta Airport. As you know the storms that blew through the south kept her from getting on the plane yesterday.

She went through multiple cancellations and was never able to rebook in order to get here in time. I asked a number of staff members if they'd like to give the presentation, they all declined so, it has fallen to me. Cara is willing to let us use her slides. It seems that that weather that came through Atlanta is coming here today. I'm glad that everyone got in this morning safely and all the speakers as well and hopefully you'll be able to get home tonight as well. I'll do my best here with Cara's slides. Fortunately, Steve Dumler is following me so any inaccuracies I say about anaplasma he can correct.

First of all, human granulocytic anaplasmosis, the etiologic agent is anaplasma phagocytophilum. It's a small gram negative intracellular bacteria. It is found inside granule sites and the organisms multiple to form micro colonies known as morulae. I think morulae is either a Greek or Latin term for clusters and blackberries come from those kinds of things as well. The distribution of HGA is worldwide although it is primarily in the northern latitudes of North America, Europe and Asia

although you will find it in Brazil, Guatemala and a few other places around the world. This was put in to keep in mind that *Anaplasma phagocytophilum* not only cause illness and infections in humans but infects our dogs, our cats. If you own a horse, you need to be worried as well.

Now, a little bit of history of HGA and Peter eluded to some of this, the first reported case occurred in patients from Wisconsin and Minnesota in 1994. It was originally classified under genus of *Ehrlichia*. In fact, it was formally known as human granulocytic ehrlichiosis. It was discovered then that the causative agent of human granulocytic ehrlichiosis was the same agent. There was naming going on at the time of *Ehrlichia phagocytophila* which is actually plural and *Ehrlichia equi*, horse and all these three were reclassified together as *Anaplasma phagocytophilum* in 2001. I think it's important to mention and perhaps Al will talk about this later that it became a nationally notifiable disease in 2000. The back end of the presentation from Cara is actually a discussion

about the CDC goes through the process of testing and reporting and then developing nationally notifiable disease reports. So, I'll try to do my best with that as well.

There are two vectors, primarily for anaplasma. As we've talked about the *Ixodes Scapularis* tick is the main vector in the Northeast and the Midwest. On the West Coast is *Ixodes pacificus*, two very similar ticks from the same genus. The life cycle of ticks is a two year process that involves four life cycle stages, the egg, the larva, the nymph and the adult. After hatching, ticks must eat at each blood stage, that's what they nourish on. And often they feed on different hosts at each blood stage, it can be quite different. So, ticks can actually feed on mammals, birds, reptiles and amphibians. They don't seem to be very discriminatory about who they feed upon. Most ticks, as I already said for a different stage or different animal host at each stage. There's also different timing of the year when eggs are released in the Spring, we see larva in the Summer. Eventually nymphs the following year in the Spring and then leading to adult, but

I think we'll hear more about that later, perhaps from Sam.

One of the things Cara wanted to emphasize was the importance of nymphs and this is, I think, true in most tick-borne diseases. These are the ones that are most likely to transmit tick-borne disease to humans and this is actually true of babesia as well. In part, this is a nymph here, very small in size, less than two millimeters, about the size of a poppy seed. I'm quite sure that someone sooner or later today will show a picture of a tick on a poppy seed bagel. They are harder to detect and difficult to remove. They often look like a spec of dirt or a freckle on a person's skin. So, they are extremely tiny. I mean, the adults themselves are extremely tiny and the nymphs are even smaller yet. So, I think, Cara's point was the nymphs are really the primary agent that transmits many of these diseases.

As far as transmission ecology, nymphal and adult ticks can both transmit anaplasma to humans but the role of particular animal species in reservoirs are not well understood unlike babesia where it is clearly the white footed mice,

this is a little more complicated. There's actually a variety of hosts, at least, what they've seen so far and these includes humans, white footed mice, foxes, elk, white-tailed deer, red deer, sheep, goats, reindeer, rodents, racoons, opossums and other mammals as well.

This was a nice slide. I've never seen this one before but I'm going to have to look this one up and incorporate it into slide decks in the future. It is a nice life cycle of anaplasma. One of the important things that come out of this slide and that Cara wanted to emphasize is that although anaplasma can pass through ticks transtately, it means it will go from stage to another, it does not pass transovarally. So, when a female tick lays eggs and if the female tick is infected with anaplasma, it cannot pass it on to the eggs. So, it has to start with the small six layer larva that will feed on an infected host. As we said, each stage feeds on additional infected hosts in order to gain blood meals and at those times they can become infected and they pass it on to the next stage transtately. And so, we can see a number of animals are involved,

humans, mice, canines, elk, deer and so forth as we just talked about. Keep in mind this transtately stage is rather important.

Now ticks have an important habitat preference. They live in wooded brushy areas and this is going to come up over and over again. I think today and a little bit about ecology and certainly Sam will talk about it. They also need humidity to survive. Certainly, mosquitoes are killed in winter months because they can't live because of the cold weather. Ticks and I'm not sure, maybe some of the New England folks could tell me if this was a good tick year or bad tick year in New England. They actually like the snowfall because they stay under the snow packs where it's a relatively nice 32 degree temperature and humidity is actually relatively high underneath the snow pack. What doesn't work well for ticks are very cold, dry winters in which they can easily become desiccated.

For us and other animals, exposure to ticks is greatest in the woods especially along trails and the fringe areas between woods and border. The ticks search for hosts from the tips

of the low lying vegetation and shrubs, an activity called questing where they come up to the edge of these brush or leaves and they stand there with their arms and mouths open waiting for someone to contact them. They then grab onto people and animals that brush against the vegetation and crawl upwards to find a place to bite and they actually attach to people near ground level. So, that's why covering up your legs is probably the most important thing.

We've seen a little bit of this already from Peter but this is a geographic distribution of *Ixodes scapularis*, again the upper Midwest, much of the East Coast and it appears to be expanding and as for Rob's question, I think we'll hear about that a little bit later. In contrast, *Ixodes pacificus* has a rather limited range, right along the coast and the West Coast and up through what appears to be Nevada, Arizona and Utah.

There was a study and Cara put this on an expansion of *Ixodes scapularis* and *pacificus*. There was a study evidently by Dennis in 1998 which demonstrated *I. scapularis* and *pacificus* in

over 1000 counties and 41 states. And then some 18 years later, Eisen and his colleagues updated his previous study. He went back to the same locations, rechecked for ticks and they now recorded 1500 counties and 43 states. So, that represents a 44 percent increase in a number of established counties with ticks. They recorded the first presence in Nebraska and North Dakota and now they also indicated that *Ixodes scapularis* is now firmly established in Kentucky, North Dakota and Ohio. So, I think the take home message is that it's expanding.

There is this nice picture, nice graph from the Eisen paper. If I have the colors correct, those areas that are black or gray represent areas that were found in both studies to have the ticks. In those areas in which we begin to see the reds, yellows and the greens represent the expansion of the territories. So, the bottom line again is that we are seeing expansion of territories of these ticks at least on the East Coast. A question to you you'll probably have here in a later slide is why does this appear to be expanding in the East Coast but

not in the West Coast. As you'll see in a couple of slides, it's proposed to be larger because of the movement of deer.

What's driving this expansion. Second growth woodland and dense underbrush. There's favorable temperatures, humidity conditions for ticks and also favorable for white-tailed deer. Many of us, I think, live in suburban environments and I think most of us have not only ticks in our backyards but likely have deer who visit our backyards. So, you can get an idea of how these diseases have increased and how we're seeing more contact between humans and the potential for infections.

There's actually extensive deforestation, deer hunting during the 18th and 19th century's. The early settlers in the United States they cleared all the land for farming and also for raising of crops and for cattle and so forth. But what's followed in that time and particularly in the last 50 years has been reforestation which has led in an increase in the white-tailed deer population. In fact, in some areas back in the 18th and 19th century, the deer

were actually eliminated. So, they've actually come back. With them has come the ticks, with that are diseases.

These are a series of studies which determined the prevalence of anaplasma in ticks. These are in different states over a period between 2001-2011. You can see the numbers range anywhere from 1.9 percent as high as 23 to 34 percent in New York State, I'm not sure where that was. You can see a wide range of studies. What it does show you is that the ticks do carry this agent.

Coinfections, I haven't heard this today but I'm hopeful that someone will talk about coinfections. Certainly, *Ixodes scapularis* and *Ixodes pacificus* are the primary vectors but they're also the primary vectors for *Borrelia burgdorferi* as well as *Babesia microti*. Simultaneous infections of *A. phagocytophila* and *B. burgdorferi* or *microti* have occurred. I think there has even been tri infections if I'm correct on that. There were also some papers in the past where the presence of more than one agent leads to one being more severe than the other.

So, there's a lot of interactions that I think are quite interesting. Less than 10 percent of Lyme disease patients have confirmed anaplasmosis infection so it does indeed occur.

This was a series of slides and I hope I can get this correct about HGA national surveillance, how the process goes. As I said, HGA is a national notifiable disease. The Council of State and Territorial Epidemiologists and CDC Program Experts collaborate to determine which conditions are nationally notifiable. They developed a list. You can find these and you can actually track these each week in MMWR. Anaplasma is there, monocytic ehrlichiosis is there, Babesiosis is there, of course, lots of arboviral diseases as well.

The Health departments have voluntarily submitted infection disease data to the CDC and the goal is to monitor, control, and prevent the occurrence and spread of these diseases and conditions. She has a series of slides showing how this works. Patient must have some kind of symptoms, goes to his doctor, and they work them up. A blood sample is taken and

based on what they may know, they suggest that perhaps we should do some testing for some potential agents. The blood is shipped out. It goes to a testing lab wherever that may be. It may be run for a battery of tests and then a diagnosis or a positive result for anaplasmosis is returned. The State epidemiologist then works with the physicians and others to write up detailed case report gathering information to try to confirm the case and then electronically, this information is sent to CDC where they are then cataloged and stored and we get the reports later on.

The surveillance case definition for human anaplasmosis is a bit complicated. It requires both clinical as well as laboratory evidence. The clinical evidence has entered reported fever and one or more of the following, headache, myalgia, anemia, leukopenia, thrombocytopenia or other hepatic transaminase elevations. There also must be laboratory evidence which must be supportive or confirmatory. These types of diagnostic tests available include IFA, immunofluorescent assay,

enzyme-linked immunosorbent assay, polymerase chain reaction, immunohistochemistry as well as culture techniques.

Now as far as HGA laboratory evidence, if it's supportive in nature, there's serologic evidence of elevated IgG or IgM. The CDC uses an IgA cutoff of greater than or equal to 1:64 and does not use IgM test results independently as diagnostic support criteria. Other supportive laboratory indications are identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination. You saw a picture of the morulae earlier. For confirmed cases, they require a fourfold change in IgG antibody titer by IFA in paired serum samples or detection of anaplasma DNA by PCR.

Alternatively, demonstration of anaplasma antigen in a biopsy/autopsy sample by IHC methods were the isolation of anaplasma in cell culture.

Cara put together several slides which discussed the surveillance summary in the United States. The CDC does large surveillance analyses evidently in blocks of five to seven years. What you're going to see, I think, is one

in five years. This was one from 2008 to 2012. 58 percent of the cases of were males. This holds true, I think, for lots of tick-borne infections, primarily males, maybe we're not quite as bright and we go to places where we shouldn't and we get tick-borne infections. Certainly, true of golfers in a rather famous study. There is 62 percent of reported patients were greater than 40 years old. There was a 0.3 percent case fatality rate and interestingly there was no fatalities among cases less than 50 years old. So, the young don't appear to be as susceptible. There's also a 31 percent hospitalization rate with 55 percent of those hospitalized reporting immunosuppressive conditions.

This is the five year data for the annual incidence of anaplasmosis in the United States from 2008 to 2012. There was a total of 8896 cases of anaplasmosis reported to the CDC during those dates. This yield and incident was about 6.3 million cases per million, persons per year. So, the annual incidence rate ranged from 4.1 to 8.7 so, overall you can see the incidence rate of anaplasmosis is largely increasing over

time.

This is a map showing you where the cases are reported, come from 38 states. The highest reported incidence rates were in Minnesota with 97 cases per million and Wisconsin was 79, Rhode Island also had a relatively high rate of 51 cases per million as well. One can look at the onset of anaplasmosis cases by month. This certainly mimics any graph you probably seen of Babesiosis where there is an increase in the Summer, May, June, July and August with a secondary blip in October which, I believe is often due to the adult ticks. This is the same similar we've seen of Babesiosis but it's also worth noting that there are cases throughout the entire year. Much like transfusion transmitted Babesiosis cases reflect a similar graph with cases throughout the year with peak times during the tick season.

The incidence rate of anaplasmosis by age group. As you get older you become, I assume, more susceptible to anaplasmosis and we see higher rates of infection. Similarly, if one looks at hospitalization rates by age group for

the onset of anaplasmosis from the same group, we see that the elderly is more likely to be hospitalized and this is not surprising, I suppose.

So, the key points from Cara's surveillance study and from this generalized study was that a geographic range of the ticks and anaplasmosis is widening. This is consistent of the expanding range of *Ixodes scapularis*. The incidence is also increasing in areas where the pathogen is endemic. Cases were most likely to occur with increasing age more likely to have life threatening complications and more likely, in fact, to be hospitalized. She wanted to make a point that the disease is likely underreported. The CDC only tracks those cases which are reported to them. So, if physicians aren't following through or it's not described, they're not getting the case report. Also, if it's in a State that is not nationally notifiable, they're not submitting those cases to CDC. Lastly, surveillance may be biased towards more severe cases. So, those that are perhaps asymptomatic and may be a problem for transfusion

transmission, we don't see. Those are her resources and this is an anaplasmosis site at the CDC.gov that you can find more information on. I'm not going to answer questions because I'm not the expert.

However, we do have an expert and he is next. Thank you. I'd like to introduce Steven Dumler. He's a professor and chairperson of the conjoined departments of pathology at Uniform Services, University of Health Sciences, Walter Reed National Military Center and the Joint Pathology Center. He's just across the street so he didn't have to come too far. He has a longstanding interest in tick-borne diseases especially those focused on rickettsial infections. He received his M.D. from the University of Maryland School of Medicine. He was trained in anatomic pathology and laboratory medicine at Johns Hopkins University School of Medicine. He completed a research orientated post-doctoral fellowship in infectious disease pathology and rickettsial diseases at the University of Texas Medical Branch. He has been on the faculty at the University of Maryland

School of Medicine and when I knew for many years, at Johns Hopkins University School of Medicine. Steve.

DR. DUMLER: Thank you, David. It's a great pleasure to be here and to be invited by Dave and by the workshop organizers. I was asked to confine my comments largely to a human granulocyte anaplasmosis and the clinical aspects of it. I've expanded it a little bit because I think there's some important messages that I wanted to get through and emphasize. Some of these will be repeated and I'll try to go through this quickly but I'm hopeful that this information will actually be a nice overlay of what we just heard.

I must tell you that I get my funding for much of my work from the NIH right here. I do also get some money from the Department of Defense to study other tick-borne infections and I do actually hold a patent for the process by which we cultivate *Anaplasma phagocytophilum* in vitro and that's used for creating diagnostic tests in many places. I get a very small royalty every year for this process. I also have to tell

you that the things I'm going to say are not necessarily the opinions of the Department of Defense for whom I work, they are my opinions.

I wanted to start out by talking about the origin of anaplasmosis or what used to be ehrlichiosis. And this was actually the very first case of human ehrlichiosis that was identified. It was a 51 year old man in 1986 who was planting trees in the western part of Arkansas. And when he returned to his home in Detroit, Michigan, he had fever, became confused, had headache, myalgia's. And he had remembered that he had been bitten by a tick during his time in Arkansas which probably isn't surprising to any of you that have been in western Arkansas. He became critically ill, he became hypotensive and went into respiratory distress. At that time, they noticed that he was very slightly leukopenic but had a very significant left shift with many bands and a very profound thrombocytopenia and elevations in his hepatic transaminases. At the time, ehrlichiosis was unknown in humans. So, he was diagnosed provisionally with Rocky Mountain Spotted Fever, was treated with chloramphenicol

and then doxycycline. He was critically ill so it took quite a long while for him to recover from this process. And as most physicians would do, they tried to prove the etiology of this by doing sero diagnosis and unfortunately as many people with this kind of process, he was sero negative for *Rickettsia rickettsii*, the cause of Rocky Mountain Spotted Fever. But interestingly, some lab technicians had noted a structure like you see in the upper figure there which is a small aggregate of bacteria inside of a vacuole in this mononuclear cell in the blood of the patient.

As a result of this, the people at CDC had seen this and was recognized as a structure that one would see in veterinary medicine in a disease called canine ehrlichiosis caused by *Ehrlichia canis*. So, they tested this patient and lo and behold he had titers for *Ehrlichia canis* that then dropped in the convalescent phase much later on, literally six months later it dropped. So, the presumptive diagnosis of ehrlichiosis by *Ehrlichia canis* was made. It was sometime later, however, that a new agent *Ehrlichia chaffeensis* was isolated from the blood

of a soldier was actually at Ft. Chafee in western Arkansas as well. And this was done at the CDC and here you can see the organism growing in cell culture which allowed us to be able to move forward with diagnostics in an unprecedented way before to actually make a diagnosis of human ehrlichiosis at the time.

Now, I happen to be a post-doctoral fellow in the laboratory of David Walker UTMB in Galveston, Texas and Dave was very well known in the field. He had written textbook chapters and things like Mandell's principles and practice of infectious disease and had just recently written an update on ehrlichiosis. He was sent a blood smear from Johan Bakken who was an infectious disease doc in Duluth, Minnesota in 1990, just when I was beginning my post-doctoral fellowship. And the interesting thing about this is, this man was an 81 year old man who was hospitalized in June 1990 and, of course, he came in on a Friday night as most really sick people do. After four days of fever, headache, confusion, myalgia's, weakness, he was critically ill at that point. His family said he had been bitten by a brown tick

about ten days before his admission. And these bacterial clusters were seen inside of neutrophils in the blood and not in mononuclear cell at that point so the arrow got misplaced there. He didn't do well, unfortunately. He died within several days. A post mortem examination, we could see these structures actually in the neutrophils. At the time, we had developed an immunohistologic test to actually identify human monocytic Ehrlichia chaffeensis and we tried staining tissues and this did not become identified by that so, we didn't know exactly what it was.

Interestingly, Dr. Bakken between 1990 and 1993 identified 11 additional cases in Wisconsin and Minnesota. And then after that with the help of a colleague of mine, Jesse Goodman, who was at the University of Minnesota at the time. We figured out a way to cultivate anaplasma phagocytophilum from human blood and the first islets were made, again creating the ability to make good diagnostics and really begin to figure out where this disease is.

I think you heard earlier, Peter

referred to the change in names of the organisms. Well, it actually was due to a complete reclassification of all the Rickettsiales that we published in 2001. And the big outcome of this, of course, was to reclassification of Ehrlichia phagocytophulus at the time to anaplasma phagocytophylum the organism we're talking about today.

I wanted to put this into perspective. I collect cases that are reported to the CDC and I've compiled them over the years. Now, this is 2011 to 2016, almost 211,000 cases that have been reported there. You tabulate them by the disease diagnosis and you can see Lyme Disease is the single or just the fraction of all the tick-borne disease. But as time has gone on, this component here which is non Lyme Disease tick-borne disease has increased remarkably. And Rickettsia, including Spotted Fever, Ehrlichia chaffeensis, anaplasma phagocytophilum, ehrlichiosis ewingii and other were non-identified ones are the largest component of this all together with anaplasma being almost as large as Spotted Fever Rickettsiosis which is the new name that we're

using for *Rickettsia* *Rickettsia* because it is probably more than a single species.

So, I'm going to focus now on the organisms that fall into the anaplasmataceae family and this, of course, includes *Ehrlichia chaffeensis* which causes human monocytic ehrlichiosis or HME and it gets its name because the organisms grown in monocytes or mononuclear phagocytes in the blood and tissues of humans that are infected. Human granulocytic anaplasmosis or HGA, caused by *Anaplasma phagocytophilum* gets its name because it grows inside of a granulocyte, we've talked about that.

There are other forms of ehrlichiosis that you may or may not have heard of. We talked earlier about ehrlichiosis ruminantium caused by *Ehrlichia ewingii* which is more genetically related to *Ehrlichia chaffeensis* but it grows in neutrophils so it looks phenotypically like *Anaplasma phagocytophilum*. *Ehrlichia muris* or *Ehrlichia muris* like agent in the upper Midwest of the United States is now known to cause disease in human. Panola Mountain *Ehrlichia* which is genetically related to a devastating disease of

cattle in Africa, *Ehrlichia ruminantium* has been identified in a very small number of individuals in the Southeast part of the United States. *Ehrlichia canis*, the canine form of this, has been identified in humans only in Venezuela, why I don't know, but only in Venezuela. In Europe and Asia, a related species *neohrlichia mikurensis* has been identified as an important cause of severe sepsis like illness in immunocompromised patients and in Asia, people with mild febrile illnesses. And recently, we discovered a new form of human *Ehrlichia anaplasmosis* caused by *anaplasma capra*. To the best of our knowledge, only in the Northeast parts of China.

Now, regardless of which species caused this disease, they really are virtually indistinguishable. They cause undifferentiated febrile illnesses and the laboratory findings can put you into the category but it's very difficult to be certain which organism you might be dealing with. We've already seen some of the epidemiologic characteristics here but I did want to point out. Among those organisms that are classified as ehrlichiosis or anaplasmosis,

anaplasma phagocytophilum, by enlarge, has become the predominant cause of tick-borne illness, not only in the United States but around the world. Here's HGA incidence over time, just drawn from CDC maps, 2006, 2008, 2010 and then 2012. So, it is increasing in geographic range, perhaps due to spread, perhaps due to recognition but I know that we're seeing a lot more now than we had before.

So, human granulocytic anaplasmosis actually has an average incidence, we've seen this of 6.3 cases per million persons over this interval. It increases with age, as we've heard, with the highest rates in those in 50 to 70 years old, more often diagnosed in men. Six percent of patients were immunocompromised, 31 percent hospitalized during this time, 6.1 percent had life threatening complications. And this is an important figure to me because when we first started studying human granulocytic anaplasmosis in the upper and Midwest with Johan Bakken, he had documented 7 percent of the individuals that developed this illness, had to go into the intensive care unit for their care because they

were that seriously ill, and that's here.

Overall, the case fatality rate has reduced over time down to 0.3 percent but it's a little bit greater in those that are elderly. It's transmitted by Ixodes species nymphal ticks and adult ticks. Here's the two that are important in the United States but in Europe is transmitted by Ixodes ricinus, in Asia Ixodes persulcatus and there are now reports of haemaphysalis concinna in China as being a competent vector for transmission as well. It is reservoired in small mammals. We know peramiscus muscosus is perhaps one of those, perhaps in servids and rheumanents. We don't know for absolute certain, the role of these in particular but we do know small mammals are likely to be the most important.

Now, I've collected more data just simply by data mining out of published literature and this is actually data that goes over a period of about ten years looking at the incidence in a meta-analysis study of tick genre and location with anaplasma. Here you can see, this is anaplasma prevalence of all ticks and you can see

North America East is the highest group out of all of that altogether but it does occur around the world. Among those in Ixodes ticks, clearly highest around here in North America and the East. And if you look at the non-Ixodes ticks in which anaplasma has been reported, typically they're very, very low, perhaps just accidental detections with the exception of haemaphysalis in China.

In human, sero prevalence data shows similar things from these meta-analysis among studies where we see actually a relatively high seroprevalence rate among all studies or among at risk populations with the highest rates over here in Europe and North America. And in cross sectional populations, a little bit lower rates there because it's going to include people that are not necessarily at risk. But here's an interesting one, among individuals who have been diagnosed with Lyme's Disease, you can see the rates are considerably higher all together, likely because of the exposure to Ixodes ticks that are the transmitting organism.

So, overall there is a 3.7 percent cross

sectional seroprevalence. But in certain parts of the United States, this can be quite high. A study that we did a number of years ago in Northwest Wisconsin using a relatively low seroprevalence cutoff, showed 15 percent of the individuals in a cross sectional study that had evidence that they had been infected by this organism. Similarly, in Connecticut, it was about half a percent to one percent of the population had been exposed.

However, the prevalence and disease in these areas is really quite different all together. In Northwest Wisconsin, there were 26 to 58 cases per 100,000 population which is .06 and in Connecticut that's 24 to 51 cases per 100,000 or about .05. So, you can see, there's a ratio of disease to seroprevalence that doesn't explain a lot. This is a potential problem for the blood supply because the people are not getting sick enough to be detected to be included in this proportion of the population. They may be donating blood and not being excluded. We've seen this already, the peak is at the time of nymphal ticks with a secondary peak later in the

year when the adults are likely biting.

I like to also tabulate data about clinical manifestations to put a face on what this is like. So, this is a study that I did with some colleagues up at Hopkins a number of years ago looking at Lyme Disease corroborated by serology and/or culture on these patients and this is what you see. Fever, about half of the patients, most of them have a erythema migrans rash, some of them have headache, myalgias but all together, it's a relatively slower progression, perhaps not quite as severe a disease. Rocky Mountain Spotted Fever, well-known as a highly severe disease. 100 percent fever, many of them have rash, most of them have rash, many on the soles and palm, headache, myalgias, arthralgias, nausea, pneumonitis, cough altered mental status. Now, compare this with anaplasma phagocytophilum. Again, similar high degree of fever, rashes is infrequent and the times where we've seen rash, it's almost always been associated with erythema migrans because of coinfection. Rash on palms and soles has not been seen to my best knowledge but headache, myalgias and nausea, vomiting,

pneumonitis, all these things are actually quite common with anaplasma phagocytophilum infection. So, it would be difficult to differentiate this from Rickettsia rickettsii infection or from other forms of ehrlichiosis. The lab findings can be helpful, as I've said before, because many of these people will develop leukopenia, they'll develop thrombocytopenia, bumps in their hepatic transaminases. So, someone that has a febrile disease in an endemic region during the summer months that has these kinds of manifestations and clinical laboratory findings, should be considered for the possibility of having human granulocytic anaplasmosis. I also wanted to point out that unlike the case with Rocky Mountain Spotted Fever, human monocytic ehrlichiosis that I'm not showing here, central nervous system involvement with HGA appears to be very, very rare. I'm only aware of one absolute corroborated case all together and I think there's some biological reasons for that that I'm not going to get into.

So, this is from the CDC study you saw earlier. We talked about the number of patients

that were hospitalized. This is actually 0.6 percent case tally rate for this particular study. Life threatening complications is 6 percent, renal failure, ARDS, meningitis/encephalitis which I'm having a hard time explaining that, pneumonia, DIC like syndrome, and sepsis like syndrome are all those things that can cause severe disease in these patients.

Now, perhaps most relevant for what we're talking about today is the natural history of how this happens. So, at some time, there is a tick bite. It takes time for the organism to be mobilized from the tick to get into the patient or into the animal and there's a grace period, anywhere from 4 to 48 hours to the best of our knowledge. At this point, the organism is transmitted into the host and now it starts the infectious process. There is a point, during which the organism is spreading, replicating, the incubation period, prior to any onset of symptoms. This can be actually variable in length of time. At some point, the organism will get from the skin and into the blood and that's

when the risk begins. And this incubation period, of course, is also during a presymptomatic time where it's potentially transmissible to ticks and potentially transmissible into the blood supply. At some point, there will be onset of clinical signs, the symptomatic phase will begin and this can be variable depending upon whether it's in a human or an animal. In humans, this is typically days, maybe weeks at the most. In animals, however, this period of presymptomatic or asymptomatic infection, can be very, very long. And why the difference between animals and humans exist, we really don't understand particularly well. Maybe Sam can comment on that.

So, finally a symptomatic period can last depending upon treatment from a very short interval of time, we've seen individuals that have been essentially asymptomatic that we've been able to show have this. Others that have been very mildly affected and the symptoms are resolved within days or others that have been sick for very, very long periods of time. And finally, they will recover. The persistence of

this in humans is not well documented, however, in animals, it is.

So, how do you diagnose this disease. Well, one simple thing to do that we did in the very beginning is just to look at a blood smear, a malaria smear, a buffy coat smear, whatever you would like, and you can actually identify those morula in between 25 up to 75 percent of the patients that have this disease. It's not 100 percent, but it's a useful thing to screen early and it can be done very rapidly so that antibiotic therapy can be done. The PCR assay is a really excellent assay for these because the organisms live in blood cells. And the sensitivity typically is between 90 and 95 percent during the acute phase of infection. Reactivity with PCR diminishes very rapidly after therapy. It doesn't appear, we've not detected any chronic phase of infection by evidence of PCR positivity after therapy or for very long after the resolution of disease. We can culture these organisms, we can do immunochemistry, but these are generally not available for most clinicians.

I wanted to talk about the main way that

we diagnose this today and that's serology. This is a study that was done by Johan Bakken looking at patients that he had seen in his practice over time. So, there's 88 individuals that came in early in the course of their illness, 32 that came in at a later time, that's this group right there and then there's a group that we discovered after the fact that had not been treated at all. What we discovered in this process that 42 percent of these individuals, this includes the people that were late when they showed up, are seropositive at the acute phase. So, what this tells us is that in endemic regions, a single acute phase serum antibody titer is probably not going to be helpful for diagnosis. 99 percent are seropositive at one month when you've gotten the acute phase same and the convalescent sample to test as pairs, so this is perhaps the best way to go. And 70 percent of these individuals will seroconvert or will have a 4-fold increase in antibody titer by that one month interval. Now, the importance of this also is because *Anaplasma phagocytophilum* is closely related with *Ehrlichia chaffeensis*, there can be false

positive tests with Ehrlichia chaffeensis infections and perhaps other related pathogens that haven't been defined. So, that one would want to consider both of these in certain regions where they both coexist such as in the Mid-Atlantic region. In these studies, we've now shown that anaplasma phagocytophilum IgG sensitivity is greater than 82 percent and IgM sensitivity is quite low by comparison, 27 to 37 percent which is perhaps, one of the reasons why IgM is not advocated as a diagnostic test.

So, here is the clinical algorithm that Johan Bakken came up with a number of years ago and I think it is still relevant today. In an individual who has been exposed to a tick or had a defined tick bite, now with acute febrile illness but an unrevealing physical exam, one would do a CBC, a differential blood count, a blood smear microscopy to look for morulae. If they have leukopenia or thrombocytopenia or morulae they would go into the S category. You would obtain blood for specific testing including serology, hopefully parent serology, PCR analysis, perhaps cell culture, start

Doxycycline and monitor the patient collecting blood at a later time for IFA testing over here. However, in this group over here if these don't exist, he would recommend observe for

hours, watch the clinical condition, if the patient is better, observe until the illness has completely resolved, if it's worse, go back to through the clinical assessment until you can completely go down this category or back over into a treatment arm over there. And this has worked very, very well for the vast majority of patients with this disease.

The drugs that are useful for treating these organisms, well actually, Jesse Goodman my colleague, told me once that these are all among those diseases that we categorize as Doxycycline deficiency diseases which, I think, is probably really salient. But Doxycycline is the main safer treatment and what is written in all the textbooks and is published. Chloramphenicol has been used in some individuals. It has possible efficacy and we don't know if there's clinical failures or not with that. Unfortunately, the organism is not susceptible in vitro, so we don't

advocate Chloramphenicol. I know that Peter and Johan put together a very nice little study and looked at Rifampin use in children because of the proclivity for some physicians not wanting to use tetracycline antibiotics in kids. And they found that in vitro, this is susceptible and that it seems to have clinical efficacy. Whether or not failures occur with this, we don't know. I have to say at the outset, there have been no clinical trials done with any of these to be able to determine really how well they work.

Alternative drugs include those in this category, the Ciprofloxacin, levofloxacin. Ciprofloxacin is not susceptible in vitro. We don't know about its efficacy clinically or whether there would be failures. To the best of knowledge, there's been only a handful of people that have been treated with levofloxacin where there was variable in vitro susceptibility. It seemed to be effective, however, the patients seemed to relapse once the drug was removed. So, still doxycycline is the drug of choice for adults and children alike. If you're uncomfortable or phantom has some evidence that suggests it would

be useful. Here's the doses in adults 100 mg orally or intravenously 12 hours, modified for children appropriately to this dosage. The duration of therapy for this should be HGA. We typically recommend it for ten days and a little bit longer for other rickettsia organisms largely because of the potential for co-infection with *Borrelia burgdorferi* which would require a longer interval of therapy. Tetracycline could also be used in similar ways and Rifampin which is probably effective could also be used in these doses and you have the handout in your thing so I won't belabor that.

So, prevention while there are no vaccines available currently for these, so we do advocate regular tick checks on people. We have at least minimal data out there that a transmission can occur within 24 hours of tick attachment but it seems to be most efficient after that interval. And the use of tick repellents and there are a variety of them that now are available including those that can be seen on this website could be used to prevent ticks from biting. Protect your pets from ticks because

they will bring them into the house and limit your exposure to tick infested habitats when ticks are active. Where protective clothing when you're outdoors such as these, and remove ticks that are attached immediately and a variety of other folk remedies as listed here, probably should not be used because it increases risk.

So, the final things I just want to say as important points are anaplasmosis is really not a rare infection at all and it can be severe or fatal in a small proportion of individuals. Why it is that way in certain individuals and not in others is something that is actively being investigated, at least in my laboratory. To prevent severe sequelae, you have to actually start empiric treatment early and therefore before and therefore you must have a clinical suspicion at outset. This includes tick bite history or exposure, an unrevealing physical exam, fever with leukopenia, thrombocytopenia and/or bumps in the ALT or AST. And the diagnosis can sometimes be confirmed rapidly by looking at a blood smear or by doing PCR testing. But the serologic testing, the mainstay, should be paired

serology, not just acute phase, one single sample that should be pairing serology which means that you have to treat based upon suspicion in many cases.

Outcomes for anaplasmosis are usually benign but success depends on the early use of doxycycline treatment and we have not seen evidence of chronic or persistent infection in humans, although we know it does exist in animals. A role for prophylactic antibiotics after tick bites has not been investigated. I was told that this is not something you would do for a Kessel infections but the evidence basis for that is completely unclear and I think it is probably something that should be investigated. There are no vaccines available but anaplasmosis can be prevented by avoiding these tick bites, protective attire, repellent use and rapid tick removal. So, with that, I'll stop and I appreciate your attention and if there's time for questions, I'll be happy to address them. Thank you.

DR. KATZ: Louis Katz, America's Blood Centers. I'm not a blood banker, I just play one

in D.C. You had a slide where you showed 4 to 48 hours for the grace period. I'm kind of interested clinically in where that 4 to 24 segment of that came from. Because as I've given advice as an ID doc for years and years, I've told people no less than every 24 hours for tick checks.

DR. DUMLER: Well, I would agree with that advice, absolutely. So, the actual data on the interval it takes from tick bite to transmission for anaplasma is based solely to my knowledge on a very small number of mouse model experiments. And so, what happens in humans is still really an unknown factor.

DR. KRAUSE: Hi I just really enjoyed the talk. I had a question that was actually asked earlier either by Sanjay or Robert both. On the duration of bacteremia with this disease. That is, is it prolonged or do we know that?

DR. DUMLER: Yes this is really interesting. The opportunity to do these kinds of studies doesn't present very often but we actually have a very large archive and we've been studying this disease for a long time. The vast

majority of the patients that we get blood samples from have been identified as likely having this disease and they've been treated empirically already. So, by the time we get a convalescence sample which is usually two or three weeks later accompanied by another blood sample to do PCR on, it's inevitably negative. Among those individuals that Johan had seen and not treated but were diagnosed retrospectively, none of them persisted for up to that three or four week interval when we got the secondary phase of blood. Almost inevitably if we had two bloods several days apart and the patient had been treated with doxycycline, it's gone by the second or third day. And it actually mimics the clinical response to doxycycline. These patients respond so rapidly, they go from feeling like I think what Johan would say is they described being run over by a truck and they might even be in the ICU. I've seen them come out of the ICU within two days back in their bed and then home by the end of the week. So, it is remarkable how well they respond to this.

To get back to the story, my sense is it persists perhaps for a very short period of

time, not more than several weeks at most before the immune response kicks in and eliminates it spontaneously. The other evidence that probably speaks to that is the fact that there are so many people out there that have subclinical infections that don't have long term consequences of which we're aware that tells us that it's probably a very limited interval of bacteremia.

DR. JAIN: This is Pawan Jain from FDA CBER. You described the treatment for the children by using doxycycline not tetracycline. Do you have an age limit on that because we don't advise below 8 years or 7 years.

DR. DUMLER: Yes, so I think it's been a completely debunked idea that doxycycline is a bad drug for children. Tetracycline perhaps but doxycycline certainly has many fewer adverse consequences. The total lifetime dosage that's been used for doxycycline and tetracyclines which is the main determiner of many of the adverse consequences in children is much lower than it had been in previous times. I'm not a pediatrician, perhaps Peter can speak to that. Even in the red book now which is the pediatric infectious

disease handbook is advocated that doxycycline is the first choice for treating all rickettsia infections including anaplasma and Ehrlichia as well.

DR. JAIN: Thank you.

DR. KUMAR: Sanjay Kumar. So, you mentioned many studies showing the seroprevalence. Do you have any clinical data in the same populations in PCR. Having conquered PCR and serology is there some relationship between the two.

DR. DUMLER: It's actually quite limited. As I said before, it's limited largely by the fact that once people are suspected to have this disease, they're inevitably going to receive doxycycline therapy so, sort of the natural history of how long the bacteremia would persist in the absence of antibiotic treatment is really kind of difficult to attain. In small numbers, it seems to be about within a three week interval. Interestingly, we did a study in animals, in dogs, transfusing them with anaplasma. Actually, it can last for months in dogs which is really interesting. I've seen Kirby Staffords work

looking at peromyscus leucopus in Connecticut and it can last for months even a year in peromyscus leucopus. Whether or not that subsequent infections or the original infection we don't know. In humans, it does not seem to persist for very long.

DR. KUMAR: So, do you think in asymptomatic cases, bacteria are gone by the time serology takes off?

DR. DUMLER: I don't know the answer to that particular question. I can tell you that we did a study in wild mice looking at PCR and serology over time and about one quarter of the mice were PCR positive, one half of them were PCR positive and seropositive. The other quarter of them were PCR negative and seropositive. So, presumably there's going to be a window of factoring followed by onset of the new response that resolves the infection.

DR. KUMAR: Because I'm sure you can see I'm thinking about blood safety perspective.

DR. DUMLER: Absolutely. And I think it's data that's lacking that would probably be very helpful to guide the principles that we would

want to apply for blood collection in endemic regions.

DR. KUMAR: Thank you.

DR. KATZ: So, we know that the quality of Lyme's serology is highly variable. Talk to me about the case definition and any validation of the serology's used or accepted as laboratory evidence for HGA.

DR. DUMLER: Sure. The predominant lab technology that's accepted for this, of course, is going to be serology. Because it's the most often used and as I've already advocated it should be paired serology. I'm not certain what state health laboratories report to CDC but typically they will rely on an IgG titer. They prefer paired serology but I think they might accept a high antibody titer, say 512 or something like that. A sero conversion would be appropriate. PCR, obviously, would be appropriate. Cell cultures rarely ever done immunohistochemistry, I think is probably only done at CDC now.

DR. KATZ: My concern is the quality of the serologic studies being done at various labs.

DR. DUMLER: Well, the quality of the serologic assays, my personal belief is generally high because they're usually conducted in national reference laboratories. There are very few clinical laboratories in hospitals in the United States that will do these kinds of assays now. So, they're done under very careful conditions in many places. There are a number of laboratories that are their own shops and they do a variety of technologies that I don't think have necessarily been cleared through the FDA or other processes as equivalent to the standard IFA procedure. A lot of these techniques are coming up now and people are applying them. I'm not certain how well they've been vetted through the same process, to be honest with you. I think the CDC has similar concerns about that.

DR. LEIBY:: Thank you Steve and thank you, I think we're staying fairly well on time and so we are at a break. Please come back at 10:50, thank you very much.

(Recess)

DR. LEIBY:: If you could please take your seats so we could get started again. Thank

you for all being on time and I think we had a good session this morning and hopefully will take a little bit more time up to lunch. Our next speaker is Dr. Sam Telford, III. Sam is an epidemiologist focusing on other borne transmitted infections. I've known Sam for many years. He received his BA in ecology and evolution from Johns Hopkins in 1983, an MS in tropical public health in 1987 and an SCD in parasitology 1990 from the Harvard School of Public Health. Following post-doctoral work at Harvard on Lyme Disease vaccine. He served for ten years as a lecturer in tropical public health there. He moved on to Tufts Med School in 2002 where he is currently a professor in infectious disease and global health and director of the New England Regional Biosafety Laboratory. It is my pleasure to introduce Dr. Telford.

DR. TELFORD: So, I want to start off with a list of things that I would like to emphasize during the course of this talk. I took David's instructions very literally. That is, I want to comment on things that are related to the discussion this afternoon on our blood supply.

So, I want to make three main points. Most of the tick transmitted infections that we talk about, even the new ones, have been present in the original sites where risk was first noted. So, on Nantucket Island, for example, Old Lyme Connecticut, Spooner, Wisconsin. These things are not new, they've been around for a long time. We knew about deer tick virus, we knew about *Borrelia miyamotoi*, we knew about *Ehrlichia muris* in these sites long before human cases appeared. So, people have been exposed for a long time and interestingly, we haven't seen episodes of deaths due to severe infection by these unknown infections. We also are ignoring, we're sort of America centric. We ignore the Eurasian literature. There we have a similar epidemiologic situation with deer tick like ticks, *Ixodes resinosus* and the infections that they transmit and in particular tick-borne encephalitis which has been known since the 1930's. It's interesting I tried looking pretty hard and I could only find a couple examples of tick-borne encephalitis as a transfusion hazard. Yet the ecology there has been long entrenched and

people have been exposed for a very long time. So, we should be taking a hint from the Eurasian literature.

Tick seasonality sort of defines when the greatest risk is for donations and particularly, if you don't have a chronic phase such as with Babesiosis or with perhaps borrelia miyamotoi that you need to consider the window period, that is when is the pathogen in the blood likely to be picked up and transmitted through transfusion hazard. That is very strictly defined between May and August and particularly June and I'll talk about that. And then finally, it's clear that transmission is increasing dramatically, mostly as a result of suburbanization and with it the difficulty with which we can manage our deer populations which are the root of all evil and I will talk a bit about that.

But, in the absence of interventions I try to take the optimistic view that we will intervene and head off an impending epidemic. But risk will certainly develop the newly expanded ranges. But these things don't develop

overnight. You can have introduction of a tick. You have an introduction of the pathogen but it takes a while for that to ramp up. So, the appearance of ticks and the appearance of new infections in ticks will take a while before they become a public health menace.

And then finally, I like to make the point to my students, risk is really an aspect of human demography. That is much more so than what's lurking in the woods. You have lots of infected ticks in the woods and have no infection whatever in the people if the personal component isn't there. That is, they're not aged, they're not immunocompromised, they're not out not checking themselves for ticks. And so, the risk to the blood supply does depend, to a large extent, on these contributions.

So, a concept that I've used for a long, long time is this of guild. A group of unrelated species sharing a common resource and so ticks and fleas and lice are ectoparasites on mice. They use the mouse as a resource. So, while Lyme Disease, spirochetes, babesia, bartonellae and trypanosomes are extremely common infections of

any mouse that you trap. You can go over to the park down the street here, trap mice. They may not have babesia or Lyme Disease but they'll have bartonellae or trypanosomes and other infections. And so, they occur in characteristic guilds and if you detect one you really should search for the other. All of these common animal hosts, in fact, all of the animals themselves including ticks have characteristic microbial guilds. The reason that's important is that you've seen some nice world maps by Peter and Steve on the distribution of the ticks that transmit things like Lyme Disease and HGA. They are worldwide in their distribution and most people don't understand that they are circumglobal in the arctic zone, that is in the temperate zone. They comprise a species complex that once upon a time, was one in the same, has been split by glaciation into smaller populations and species becoming things such as scapularis and ricinus and Ixodes persulcatus.

I distinguish the northern population of scapularis as distinct because it bites humans as nymphs and scapularis does not bite humans as

nymphs at least the ones of the southern part of the U.S. There's a very peculiar original distribution of Lyme Disease cases. It was greatly localized to what we call The Terminal Moraine. These are sites which are heavily influenced by the retreat of the ice sheets. It is clear that as the ice sheets covered the land masses, the infections, the ticks, the mice, the animals all moved southward and are now or after the retreat of the ice ages moved northward and colonized the very edges of the ice sheets first and those are the sites of the most ancient populations.

And so, our working hypothesis has always been that if these ticks were once a globally distributed prior to the ice ages what they were carrying before the ice ages should be seen after the ice ages and wherever these ticks are. And so, what we see in Eurasia should be found here in North America as well. I've used that concept very successfully and looking for things, that's another story entirely. Others have eluded to the fact that there are a number of infections transmitted by deer ticks

themselves. Of note, there's a new terminology for Lyme Disease, it is validly published and therefore by the bacteriologic code, we must use it. It's not appreciated how extensive that microbial guild is in the sheep tick, *Ixodes resinus* which is so closely related that an expert like me can't tell them apart morphologically.

And so, there are all of these things and of this list there are agents that we have not yet looked for here in the United States. It's not axiomatic though that we will find them. That is, *Ehrlichia muris*, for example, has been discovered in the upper Midwest. We've beat the bushes in New England and have not found it in animals or in ticks. So, there may be something peculiar about the northern upper Midwest. We use this concept to look for a tick-borne encephalitis virus in the mid-1990's and very, very quickly found it and I'm particularly proud of that because the Yale arbovirus research unit, which was the premiere arborvirology unit in the country, looked at thousands of ticks during their original Lyme arthritis investigations by

Alan Steer, and found nothing. It didn't take me very long to find virus in deer ticks. This is distinct. There are two lineages of what is being called Powassan virus and, in fact, I will predict that eventually it will be considered to be distinct. It's ecologically distinct.

Powassan virus is maintained in wood chucks and wood chuck ticks. Deer tick virus, as the name suggests in deer ticks and their hosts. Back in the mid- 1990's, we couldn't find cases and we thought, well so what. Tick-borne encephalitis virus proper exists as three different sub types in Eurasia. The central European encephalitis subtype has a great asymptomatic to symptomatic case ratio. That is, most cases are asymptomatic and we just thought, well with the deer tick virus it's the same, so what. I wasn't gratified but I was surprised to see that it's now been incriminated as an emerging cause of meningoencephalitis in the U.S.

So, that was strictly because I went looking for it because I knew tick-borne encephalitis was a prominent member of the microbial guild in Eurasia. Same thing here with

Ehrlichia muris first described in Japan in the mid-1990's and all we had to do was go back to our archives and find Ehrlichia muris in deer ticks in the 1990's, long before people found these things infecting humans. The prevalence of infection in Spooner, Wisconsin is very similar to that of anaplasma phagocytophilum and so it suggests to us that people were, as Steve pointed out, ehrlichiosis presents as undifferentiated febrile illness. Whether it was attributed to anaplasma phagocytophilum or simply atypical anaplasma was clearly the case that people weren't distinguishing the fact that there were two different Ehrlichias in Northern Wisconsin causing this febrile illness.

So, these things are under our noses all along. The same thing Peter mentioned, the history behind borrelia miyamotoi disease. And here, this is a paper from 2001 and it's very clear that this spirochete was present in fairly good numbers in four states around 2001. And we only found infection in humans much later on. The reason for that being that the clinical presentation could be very similar to that of HGA

or to Lyme Disease without the rash.

So again, these things have been under our noses all along and the question really becomes in these sites where transmission has been longstanding, surely there have been people who donated blood and had the potential to pass this on and yet we haven't detected it in the interim. So, the question really becomes is it really a probability dependent thing where only now are we going to see these things because there's more and more transmission over a larger area or is it simply because it's going to be a very rare event. That's where the biology comes in. Things such as what is the infectious inoculum. How much of a window of infectivity is there for the donation hazard. Those are more critical questions.

So, I want to sort of focus in on something more useful which is I was at the original Red Cross meeting when we discussed Babesiosis and what we might want to do about it for the blood supply and one of the things that emerged is a history. Ask a directed question, have you been in an area with deer ticks, have you

had Lyme Disease, have you had Babesiosis. A similar thing might be considered for the tick-borne infections in general at least here in the U.S. That is, they are seasonality of transmission is so striking, note that for all of these infections, for Lyme Disease, for anaplasma, for Babesiosis, they're all the majority of the infections, 80 to 90 percent of all the infections are in the middle of the summer and particularly in June and July. That's when transmission is occurring, that's when the nymphal stage of the tick is out. It will start around Memorial Day and it will cease somewhere around the middle of July.

The infection rates are interesting. You have a range. If you do a met analysis though, and look from site to site, there's no real statistical difference between sites in terms of so called infection rates. What is even more interesting is that generally, at least for Lyme and for anaplasma maybe for deer tick virus as well, the adult tick as doubled a chance to become infected and therefore the prevalence of infection, host seeking ticks is doubled. Yet,

we don't see much action when the adult tick is around that is in the cold months. And so, the discrepancy between the infection rate and ticks reflects empiric epidemiology, that is, clothing. People are dressed differently in the winter time or in the cold months as opposed to the summer. The tick is so much smaller as a nymph. That's a nymphal deer tick and that's a penny, that you can't see it and promptly remove it before the tick has had a chance to undergo what is known as reactivation or so-called grace period and transmit in an infectious inoculum. And then finally, the inoculum is very poorly studied.

Again, this is really one of the places where we really ought to be focusing on in the laboratory is what is the potential, what is the lowest inoculum that causes disease for 50 percent of the cases. That's a loaded question because you're limited in the laboratory to things which are very nonatypical. You've got your inbred mice, they're all the same age and mice are extremely susceptible anyway. You can put a minimum limit or a maximum limit but you

can't capture the variability in the inoculum and how that affects the course of illness whether someone is asymptomatic or clinical and whether they have severe disease as opposed to mild disease.

The one exception is *Borrelia miyamotoi* where it appears as if the peak of cases appears in August and that is coincidence when the larval ticks emerge. They hatch in mid-July through September as opposed to nymphal ticks which emerge end of April, reach a peak in June and disappear by the middle of July. So, this is interpreted by the suggestion that was originally described by Derwin Fish and group when they first found this in the United States was that the infection is inherited by the offspring, transovarial transmission occurs and therefore the larva emerge from eggs infectious. Therefore, that's the one exception to this idea perhaps using seasonality of transmission as a key to understanding risk to the blood supply.

Steve already mentioned reactivation or what we call the grace period that these pathogens are adapted to long periods of time

without feeding. If they were to use the metabolic resources of their host the tick, during the eight months it takes when they're acquired in August and September and they have the next chance of getting out of the tick in May or June, that's eight or nine months. If they use host resources, they would form a selective disadvantage for the tick. So, what they do is they go dormant. The Lyme Disease organism up regulates, it changes its code. There's really interesting gene regulation studies on what happens in those first 24, 36, 48 hours. Babesia microti is even more interesting in that it survives that period as an undifferentiated sporoblast. And when the tick achieves a new host, body heat stimulates that also to start developing and it takes 56 hours or more to have infections sporozoites develop from that blast. Same with the anaplasma, it really is 24 to 36 hours but nothing in biology is black and white. You can have instances of transmission earlier than 24 hours. In fact, the early Lyme Disease studies that were done by Joe Piesman showed that before 24 hours, one out of twelve animals became

infected when the ticks were removed at 12 hours. 20 percent became infected at 24 hours, 50 percent became infected at 36 hours and all became infected at 48 hours. So, it's a gradation in risk but it still begs, it tells you that you need to remove a tick promptly. The adult deer tick is so much bigger, people find them and remove them in time. For tick-borne encephalitis virus including Powassan virus, a member of the tick-borne encephalitis complex, that doesn't seem to operate viruses there in the salivary glands and is infectious.

So, I want to comment on the fact, I know Peter called for the need for more studies to look for pathogens in ticks and in reservoir hosts. But the fact of the matter is, there are plenty of things that we know about that we have yet to identify as human hazards. *Babesia odocoilei* is actually the most common babesia found in deer ticks throughout the East Coast, coincident with the range of white-tailed deer. It's easy to grow, we get it out of dairy, you just put in media and it replicates very nicely. You can make nice IFA antigen out of it. And zero percent react to

Babesia odocoilei. It means that this agent doesn't even infect humans to the point that you get an antibody response.

Whereas, there is something else, *Babesia divergens* or what is called MO1 *Babesia* which is present in a large number of places and we'll talk about that in the next slide. And then finally, obviously in the same set of people, there's a good reactivity to *Babesia microti*. Well, cottontail rabbits like deer are now pests in people's yards. They are widely distributed, they can reach humongous densities. 15 per hectare and we knew for a long time that they maintained *Borrelia burgdorferi* or *Borrelia burgdorferi* with *Ixodes dentatus* which is a relative of the deer tick between rabbits and their ticks as sort of a hedge against extinction. If deer ticks were to disappear, you would always have *Borrelia burgdorferi* in the environment because it was maintained between rabbits and their rabbit feeding ticks, they rarely feed on humans. This infection, *Babesia divergens* or *Babesia divergens* like infection has caused a disease in humans that is known as MO1 Babesiosis and it's

extremely prevalent in cottontail rabbits on Nantucket Island, yet we don't see beating of bushes on Nantucket and have never found a human case.

It's not that there's no opportunity. I say that rabbits and their ticks mean nothing to humans but in a study we did in a population off the coast of Maryland here, it looked like *Ixodes dentatus* actually did contribute a small number of ticks to the point of approaching that for *dermacentor variabilis*, the known vector for Rocky Mountain Spotted Fever. So, it's not that people are not getting exposed to *Ixodes dentatus*, this is *Ixodes dammini* nymph, *Ixodes dentatus* nymph, they look very, very similar. But they certainly are infected and interestingly, the deer ticks that come off of rabbits are also infected with *babesia divergens*. So, the question is why don't people get infected when they're clearly exposed.

I kind of laugh sometimes when people say ticks are so full of pathogens and see all of these nice new studies coming out with whole genome sequencing and describing the microbiomes

within ticks and employing that there is a hazard to human health. I go, so ticks aren't allowed to have a gut flora like everybody else. If we took our fecal material and put it into mice would that not cause pathology. So, it is no surprise that there's a huge number of bacteria within ticks and to infer that these are hazards to human health simply because they do transmit pathogens to humans is not quite clear. The important thing is to always, always, always check, it gives you an awareness. We're looking for these things, oh here is an unexplained case, maybe it's due to that. So, that's where the proactive version can come in where you say, oh I know babesia odocoilei should be there, oh I know babesia divergences should be there and if you have a zebra in the clinic then you test for those. But until someone publishes a case report identifying that agent as an ideologic agent, they're just symbionts of ticks. They're just gut flora of ticks.

So, we spent a lot of time on deer ticks but it's not just deer ticks now, it's the Lone Star tick which is greatly advancing its range

perhaps as a result of climate change. They are the notorious pest tick from about here down to about north of here, New Jersey and Long Island, down to Florida and across to Texas. All three stages are aggressive. Unlike deer ticks they're not ambush predators. These guys have eyes. They think nothing of walking from me to you in the matter of a couple of minutes. They orient toward big objects. They have long mouth parts, they hurt when they bite. Like deer ticks though, deer are the main hosts for developmental stages. The female tick takes a blood meal from a large animal, usually deer, and lays 3500 eggs as opposed to 2000 eggs for deer ticks. The larva emerge in late summer and then over winter and become nymphs the following Spring. In the Spring, you have both the adults preceding them slightly, they start appearing middle of April and the nymphs appear sometime towards the middle of May. You'll have a coincidence of the adults and the nymphs in that time between mid-April and mid-July or so and then they disappear.

And then you have this horrible pest, what we call seed tick in the South. These are

masses of larva on a lint roller masking tape. Each of these spots has something like 300 larvae. You can walk into a pile of these and have them crawl up your leg. They'll concentrate around your belt and you use a credit card to scrape them off because they're so numerous. This is a well-known condition in the South, called seed tick. Fortunately, they don't seem to transmit anything to humans but they are very, very aggressive. Interestingly, they are now linked with what I consider to be the worst disease of all which is an allergy to a sugar, a red meat allergy. Lone Star ticks appear to be epidemiologically linked to these cases of an immediate type reaction to red meat. The basis for that remains unclear, although, the sugar that is the target is actually a normal component of most ticks.

Rabbits and other animals, racoons feed the larva and nymphs. We do think long distance transport is happening but galliform birds, things like quail, are not known to migrate. So, how they get from a Long Island to Massachusetts is not clear to us. They're very, very, micro

habitat dependent which means they're easy to model in terms of their potential spread. This is their current distribution. This is what it's supposed to be like 20 or 30 years from now under typical climate change scenarios. And they are known vectors for monocytic ehrlichiosis, Ehrlichia ewingii ehrlichiosis, Masters disease a Lyme Disease mimic of unknown etiology, we don't really know what causes Masters disease. Tularemia, Spotted Fever or as Steve points out, Rickettsiosis, Spotted Fever like Rickettsiosis and then two viruses that got a lot of attention in the press because they caused so-called hemorrhagic disease. Bourbon virus and Heartland virus, both from the Midwest and linked with Lone Star. Whether those will ever show up, up North or in the expanded distribution of Lone Star ticks remains highly speculative.

Does the introduction of the Lone Star ticks imply new risks, it's not clear. We've been studying Prudence Island since the early 1990's. It's the northern most established population of Lone Star ticks. It's been there since the 1960's. These people are horribly

effected. They have Lone Star ticks, they have deer ticks, they have dog ticks. The people there are miserable. They have most tick-borne disease of any population that I know of. And then Cuttyhunk Island at the end of the Elizabeth Islands and Cuttyhunk had no Lone Star ticks prior to 2010. Bam, they appeared, now they're the most aggressive, the most common tick out there. They have similar numbers of dog ticks and deer ticks, maybe fewer on Cuttyhunk. We've been doing some sero surveys to look at the burden of disease on these islands comparatively. And old Lone Star tick population versus a new one and found very interestingly that one island had residences who were highly reactive to an LPS antigen for the Spotted Fever group Rickettsia and the other one didn't. That suggests to us that there is a certain lag time before we have an issue with a disease.

Where did this come from. Well, we changed the landscape, we chopped down the forest, we changed it to farm and then we let it go back to forest. We are now increasingly developing and using that reforested material in

this process called urbanization. And as a result of suburbanization, we have a hard time controlling deer. As a result of our changes in the landscape, the American dog tick is now endangered in a lot of places. The grassland has disappeared and the hosts themselves, dogs used to be the main source for the reproductive blood meal. Now we're using topical antiparasitics and the ticks have to depend upon skunks and racoons which are episodic in their population density because of rabies and distemper. Dog ticks seem to be disappearing from New England, nonetheless, they still maintain infections of local importance such as on Martha's Vineyard with tularemia.

The distribution is certainly changing. You saw this map before. Lyme Disease was once a circumscribed to very small sites in the U.S. and now has been greatly expanding across the Northeast corridor and the upper Midwest. We see this happening on a local level. Al DeMaria will probably talk a little more about this but it's clear how quickly cases march across the landscape in a span of a few

years. I see this as associated with, not proven, but highly suggestive with respect to where you can and cannot hunt deer. That is, in the orange areas, that's where there's a 500 foot setback from hunting because you cannot discharge your firearm within 500 feet of an inhabited house without written permission. So, deer are getting very difficult to manage in Eastern Massachusetts and I think it goes hand in hand with our increasing risk. So, obviously things are going to happen in the next ten years, the next twenty years as suburbia grows and grows around a major metropolitan area.

Landscape changes thought have hit a plateau. It's looks like the forests are now reforested. They're not going to be any more changes in the forest but will change is development. Obviously 1971 versus 1999, a lot more suburbia out there. So, the big issue there is where people have intruded into the new forested habitats, they're disturbing longstanding sites of transmission. The Soviets thought a lot about infectious disease transmissions. They came up with the idea of

natural modality, natural focality, that these infections exist in longstanding foci. They can be isolated, they can be so small that you would have to be really unlucky to step in one of these things. They can be as small as this room or they can be much larger and they comprise optimal, physical and biological associations. They are not randomly or evenly distributed and the new foci developed largely as a result of introduction of new hosts or because amplification occurs in these little foci across the landscape and this is what happens later. It's much harder to step in something here but it's almost guaranteed you're going to step in something here.

So, that's the pattern that we see across Eastern North America is coincidence of landscape changes followed by demographic changes, changes in suburbia which allow us to contact more of this. This is obviously going on and, in fact, there's pretty good evidence now that at least babesia microti, this is probably what has happened across the New England landscape.

It's a whirlwind tour of what I would normally give a full year course on in a school, NIH has generously supported our work. We have a study with Adriana Marques here at NIH on persistent Lyme Disease and some foundations have been picking up the slack. I'm training a new generation of field biologists with me and my wife does all of the molecular biology and that's what has allowed us to remain productive in a time of diminished research funding. So, with that, I'm happy to, I probably don't have time for questions but I understand I'll be on the panel later.

DR. KRAUSE: My name is Peter Krause. I have a simplified understanding of climate change and that is as things heat up, they dry out. And ticks like to have moisture. So, what is your thought about the general trend in terms of ticks and climate change. So, I would think that they would essentially be moving North.

DR. TELFORD: In general, you're correct. The deer ticks, especially, our neighbors to the north, the Canadians, will get what we have in Massachusetts 50 years from now. We'll become much more like our southern

neighbors down in Virginia or North Carolina or maybe Florida and we'll see less Lyme's Disease. But, the Lone Star tick, which requires for its development, warmer temperatures, may develop faster in northern sites, notwithstanding the fact that they're even more sensitive to moisture loss than deer ticks so it may be a complete wash with them. But the more important thing is that all of these things are so highly focal in their distribution, that you could have one part of a community in a wet area, have lots of ticks and the rest of it is so dry that you won't have any ticks and have this across the landscape. So, it's hard to sort of predict overall, but in general, you're right. As things dry out, these ticks don't like drying out and we'll have less transmission where we have it now but those neighbors to the North may have more.

DR. KRAUSE: Thanks,

DR. LEIBY:: I think it's only appropriate at this point, as we've had a lot talks about epidemiology, about ticks, tick-borne infections, we now move on to some what I would say is real life issues, particularly at

the State level. So, I'm calling upon Al DeMaria to give our next talk. Al, many of you know, serves as the medical director of the Bureau of Infectious Disease and Laboratory Sciences in the Massachusetts Department of Health. He is also the State epidemiologist for Massachusetts. He's a graduate of Boston University and Harvard Medical School. He's trained internal medicine at Mont De Fiere Medical Center in the Bronx, New York and infectious disease at Boston City Hospital and the Boston University School of Medicine. Prior to joining the Department of Public Health in 1989, he was an infectious disease consultant in private practice and prior to that, on the staff of the Maxwell Finland Laboratory for Infectious Disease and Section of Infectious Diseases Boston City Hospital and Boston University School of Medicine. It is a great pleasure to introduce Al DeMaria who will talk about real issues at the State level.

DR. DEMARIA: Thank you, David. I'm not sure if I'm operating in another world. I'm not sure if it's the real world but it's state government. What I want to do is frequently site

and utilize public health surveillance data. I think it's very important when doing that, that you understand where those data come from because there are certain limitations inherent in the way we do public health surveillance. That's not to say that there aren't strengths to the public health surveillance data that can be used to help us make policy decisions. And I think it's important to recognize in the federal system, all authority for public health surveillance resides in the states because it's not explicitly covered in the Constitution. The Council of State and Territorial Epidemiologists was actually created in the 1950's by Alexander Langmuir at his request to try to develop a consistent national surveillance system by getting all the states together and agreeing on how this would be done. What would be nationally notifiable and how it would be defined. Because if people were using different case definitions you couldn't have a coherent national system of surveillance.

So, once the Council of State and Territorial Epidemiologists agree with colleagues at the CDC to make something

nationally notifiable, there's an inherent expectation that they'll make that condition reportable in the states. Because if it isn't reportable in the states, they won't have the authority to collect data. Once a condition is made nationally notifiable, then the States report those data to the CDC as you saw earlier in one of the earlier presentations. States may make many other things reportable that aren't nationally notifiable. Those may or may not be transmitted to the CDC.

So, the disease reporting pathway is that healthcare providers, facilities and laboratories report to county local health departments usually in most states and then they report to the state health department which then transmits data to the CDC. And that's sort of the way things work. And to understand this better, you have to understand that now it's mostly laboratory generated, the states have developed electronic laboratory reporting systems, the local, the county, the state health department gets laboratory results. They're then investigated usually on the local level. So, the

local health departments have to have the resources to do adequate investigation of these laboratory reports to get reported to them. Very little is reported from the practitioner directly, but still in the case of Lyme Disease, erythema migrans is reported as a clinical indicator of disease by practitioners.

So, there's a division of labor in this system. Most of the actual collection of data for those case report forms, come from the local level. And then, data are consolidated at the state level and then data are reported onto the CDC. So, what you see in the MMWR is a result of all that. Now all of that is subject to resource limitations and actually case definition limitations at each level whether the case definition can be met with the data at hand. In Massachusetts, we have extensive regulations that cover all of this as most states do. So, in each jurisdiction, things are done in a slightly different way. Again, we are in a federal system, that's how things work.

So, now I want to Massachusetts as the micro caecum of this. We're unusual compared to

other states in that we have 351 independent health jurisdictions. Every city and town is its own jurisdiction and theoretically is responsible entirely for the public health surveillance at that level. Most other states have county health departments. Massachusetts has 12 percent of all the local health departments in the United States but only two percent of the population. That's the reality that I deal with. Most of surveillance is now driven by laboratory reporting so those come to the states, they get sent out to the local health departments electronically and then the local health departments send back data to us.

Lyme Disease has been reportable in Massachusetts since 1985 as has Babesiosis. Anaplasmosis was made reportable in 2003, borrelia miyamotoi in 2013. Massachusetts may possibly be the only state that is actually reportable. And Powassan is implicitly reportable as in many states. So, all arboviruses are reportable. And then national modifiability is presented there. So, what do you see in terms of the data that are available

depends on when it was made reportable in most states and when it was made nationally notifiable to the CDC.

Babesiosis was made nationally notifiable in 2011 when it was reportable, I think at that point in 24 states. This is the recent reportability of Babesiosis in the states. A state that says it's implicitly reportable is saying that an unusual disease and Babesiosis would be relatively unusual and Alaska would be reportable on that basis. Now, Babesiosis is reportable in 41 states. Not all jurisdictions, even though it's nationally notifiable, it's not reportable in a certain number of states. I think the most pertinent one to the discussion of Babesiosis in risk is Pennsylvania, which is sort of in the middle of a higher prevalence, a higher incidence area for Babesiosis.

Anaplasmosis is actually more widely reportable because again, in many areas ehrlichiosis and anaplasmosis were made reportable in the early 2000's and nationally notifiable in 2008. So, if you look at trends in Massachusetts in Lyme Disease, we have thousands

of cases. If the CDC is right and we only record about 10 percent of the cases, we have tens of thousands of cases which I don't doubt because it's become part of the daily existence. Sam and my colleagues at the Department and I, do a lot of community tick talks, as they're called, talking about tick-borne disease. You hear the stories of people out there doing tick checks every day, they're talking about Lyme Disease every day, it's talked about at the schools and PTA. It has just become part of the existence in those communities.

Likewise, Babesiosis has increased markedly. Some of this is surveillance artifact in terms of reporting but not much of it. Much of this is actual increases in the incidence of Babesiosis over time. So, now we have routinely over 500 cases reported in a typical year up from about 50 cases a year back 10 - 15 years ago. We have reported cases of confirmed very probable in this case, anaplasmosis again, with sort of double digit percent increases and 2016 hasn't been fully counted yet. I'm sure we will be going up probably another 10 to 20 percent by the time

the counting for 2016 cases. Because again, there is a relatively complicated process involving local and state public health here and they are still collecting information on cases that haven't been officially classified yet.

If you look at this in another way in terms of what's actually reported to the state in Massachusetts, there are over 10,000 cases that potentially could be Lyme Disease cases. They may get revoked, in other words, we can't tell if they meet the case definition, but many of them remain suspect and many of those are Lyme Disease cases that you won't see in the national data because revoked and suspect cases aren't reported to CDC, only the ones that meet the national case definition. That's true of Babesiosis as well. Many of them are revoked, that is we don't count them as cases with any classification but in point of fact, many of those may be cases, we just don't have the second IgG that would be required, the convalescence serum IgG that would be required to count them as a case with a 4-fold change because then the cases of Babesiosis and anaplasmosis, when they're diagnosed serologically they do

require a titer change over time. So, again we're looking at a subset of the actual cases when we're looking at the surveillance cases. And likewise, that's true of anaplasmosis. As more and more PCR technology is applied to testing, we're getting more confirmed cases. But again, the testing has to be done at the right time in the course of the infection to actually be positive.

And then we're looking at this statewide and what we see is diffuse risk statewide but certainly not uniform risk statewide. So, there's a focality to the risk of diseases. And there's this progression from the westward and northward we've observed over time. Now, one of the ways I think the data can be used is in this way. This shows the age distribution because 2014 data, so one year data. The age distribution of Lyme Disease, Babesiosis and anaplasmosis. All members of the guild, as Sam would call, the guild of infectious agents in ticks. So, I would say that the children who are presenting with Lyme Disease, are getting bit by the same ticks that are transmitting anaplasmosis

and Babesiosis that are only being recognized in the older portions of the population. So, I think this gives us an indication of how much subclinical infection there is because we're not seeing it in the kids. Because either they're have subclinical infection which I think is primarily true of Babesiosis or in the case of anaplasmosis, they're having subclinical infection where they're Lyme Disease or suspected Lyme Disease is getting treated early before they can manifest their clinical anaplasmosis.

So, I think it's helpful to look at this as an indicator and potentially use in modeling, the potential for subclinical infection in the population. Because if you just look at the ratio of Lyme Disease to Babesiosis and anaplasmosis by age group, I think it does represent a measure of subclinical infection that might be helpful when assessing risk not only for anaplasmosis potentially some day for the other infections that are emerging and becoming more prevalent. A way of looking at what is the potential for subclinical infection in blood donors in that younger age group.

The other thing is looking at Lyme Disease and of the other tick-borne disease by when they manifest during the year, I think, again looking at this in terms of the potential for co-infection between these diseases and how recognition might be affected by the fact that Lyme Disease tends to occur earlier than Babesiosis and people present with Lyme and get diagnosed with Lyme's Disease when they also have co-infection. We're very interested in co-infection. One of the results of the workload in terms of looking at Lyme Disease and getting all of the parts together to get reported cases is that we're at the point of not counting Lyme Disease cases anymore. Because why count thousands of cases. We know it's out there, we know it's huge, we know that nobody does anything with those data and we know that it's not generating any policy decisions putting resources to addressing tick-borne disease, so we're going to look at other secondary sources of data like all pairs claims data and other indicators, laboratory data alone, to try to model what's going on with Lymes Disease in

Massachusetts rather than trying to collect so much information on individual cases of Lyme Disease.

But one thing we're going to continue to look at is co-infection because we will be able to identify these cases because they're almost always clinically apparent in one of the cases of disease. And Babesiosis, if you remember the map I showed earlier, Babesiosis and Lyme Disease, co-infection tends to occur where Babesiosis occurs mostly in Massachusetts. One thing we've observed in all of these data is the emergence of the metro west area as I think now is actually at a higher risk than Cape Cod. It used to be 25 years ago when cases of Lyme Disease presented, people said, well when did you go to the Cape. Now we don't say that anymore because Lyme Disease is occurring everywhere in Massachusetts and, in particular, in the metro west area. We're looking at the characteristics of co-infection now as an important indicator of the morbidity of tick-borne diseases in Massachusetts and looking at that as well with the Anaplasmosis. So, I think this is another way we can use surveillance

data to inform decision making around a lot of other aspects of tick-borne disease and potentially transfusion risk as well.

As I said, *Borrelia miyamotoi* is reported, is very controversial. Most of the people I work with did not want to make a reportable and I said I think we should because most of the reports are coming out in Massachusetts and I think we should at least try to look at it. So, we had to invent our own case definition which we try to model on the other tick-borne diseases. But what it's resulted in is a number of suspect probable and confirmed cases. Again, those suspect cases, it's very difficult to get all the information, especially convalescence testing results on these patients leaving us with a lot of suspect infection. But I think this is another clearly emerging and Dr. Krause told me years ago that we would see this stepwise emerging infection. And Sam's been talking about this as well, I think this is what we're starting to see with *Borrelia miyamotoi*. Of course, nobody was testing for it prior to a few years ago but I think our expectation is that

this will be, and the series of miyamotoi cases published mostly out of Massachusetts, suggests again that the distribution that the risk of infection comes from the nymphs.

These are the total reports of miyamotoi against the confirmed and probable as in the line and the columns represent the total cases. I think the total cases do represent what is actually doing on that we can't confirm or make into probable cases. As we get better at diagnosing this we get better at doing surveillance for this we'll see very similar results as we've seen. I'm going to ask Sam this question, is the late cases that are occurring representative of the capacity for adult ticks to transmit this borelia similar to what we see with anaplasmosis. And then the age distribution is very similar to the age distribution for Babesiosis and anaplasmosis suggesting either we're missing cases in kids or the kids are just skipping along without symptoms, another question we might address during the panel.

And the Powassan, we've heard about already we're starting to get reports in

Massachusetts. It's been reportable, we're not sure we're getting all of the cases. As we're bringing on the reference laboratories more and more that are doing the testing, I think we're going to see that and we're going to see an increasing number of cases in Massachusetts and the United States. This is what we have so far. Many of the cases reported to us, we reported them to *piantiadosi* cases that were reported in the *Annals of Internal Medicine Journal*. What's interesting here and again a question I would pose to Sam, 12 to 1 male predominance in the cases that have been recognized so far. When we map these cases out, we see most of our *borelia miyamotoi* cases in southeastern Massachusetts. Now, that may be because the laboratory that's doing most of the testing is sitting over here. But what's interesting is Powassan northerly and I think this has been a similar distribution of Powassan cases more northerly has been reported by the CDC as well. That's another thing that I would like to get into during the discussion.

And then, Steve Rich of the University of Massachusetts, the Laboratory for Medical

Zoology test ticks that people pull off them or their companion animals and tests them for a variety of infectious agents. This gives us an indication, not what's infecting people but what's affecting people in terms of the ticks that might be transmitting infection to them if they unfortunately didn't get them off early enough. We see all of these pathogens in Massachusetts. Ticks tested in 2015-2016 still obviously Lyme Disease spirochete is predominant. But there's substantial numbers of these ticks that are positive for the other pathogens both the ones we've recognized for a while and the ones we're just starting to recognize. So, we're starting to look to this kind of data to help us come up with risk models for the population in Massachusetts. So, let me stop there and I think we'll go to the panel. Questions.

DR. LEIBY:: If there's no questions for Al, I would ask all the speakers from this morning to please come up and have a seat. Brian too, wherever you are. Okay, thank you. You can see the list of questions that were provided to the speakers and what we'll try to do in the next

half hour or so, we'd like to go through these and we'll see how we do on the questions, if we cover all of them, portions of them or if there's one that seems particularly interesting to the group. So, I'll pose the first question to the panel. Do the trends in the epidemiology of tick-borne agents suggest significant risks for infection of blood donors, blood recipients and blood safety. Anyone want to take that?

DR. DEMARIA: I just want to reiterate that I think one thing that we should look at is sort of the distribution of cases by age and as an indicator of how much subclinical infection is out there. There are not too many ways we can determine that except for sero surveys and other things that a lot of resources. But there are a lot of data out there that might be amenable to looking at what the probability is that there are people with subclinical infection that are getting bit by the same ticks that transmit Lyme Disease but aren't presenting in the same way as those individuals.

DR. KRAUSE: So, just a comment on that. We did a study of Babesiosis on Block

Island. We've been doing that for a long time, a number of different approaches. But one was to accrue cases both through working with physicians there so we could get symptomatic infection but we also have done biannual sero surveys. And with that biannual sero survey, we've identified people who had initial negative serology in the Spring and then positive babesia serology in the Fall and it reported no illness during that time. And so, we were able to collect data that would tell us about both symptomatic and asymptomatic disease and from that what we found was about a quarter of adults and about half of children were asymptomatic.

So, I think that it's just one study but one approach to this is to do careful epidemiology and that was over a ten year period. So, one can do careful focused epidemiologic study in one area to get some better idea of that ratio that you talked about.

DR. SPENCER: Yes, I would suggest that that ratio might be of inapparent to apparent cases is actually perhaps quite a bit higher. The American Red Cross has been testing blood donors

in Connecticut and Massachusetts for about 15 years now and over much of that period using very systematic sampling. One of the things that I've done for a few years is compare the sero prevalence in our donors and contrast that with the state surveillance data in Connecticut at the county level. So, this is not quite as granular as at a given patient level but that ratio is consistently about 100 to 1 greater fold evidence of infection in the donors compared to what actually reaches the attention of public health authorities.

DR. TELFORD: I do have one comment. One as an interesting aspect of infection biology that is the possible age related susceptibility and sex related susceptibility as Al pointed out with Powassan virus, the 12 to 1 ratio of symptomatic cases with females being apparently very, very rare for them to get it. But the other point as an epidemiologist Lyme Disease was very, very striking in terms of its age distribution where you have a bimodality where there's a dip in incidence and prevalence among people in their teen and twenties. They don't seem to be exposed

or they don't seem to get infected. The relevant point for transfusion medicine as those individuals who are younger than

are probably not going to be part of the donation package anyway. So, despite the interesting aspects of the infection biology, practically speaking, we need to focus on those risk groups who are actually donating.

DR. KRAUSE: Just one comment on age distribution. One of the confounding variables is that children get febrile illness as non-specific febrile illnesses far greater than adults do. So, an adult comes in with fever during the summer time, they're going to be worked up in a greater percentage than children because there's so much noise out there in terms of febrile illness. So, I'm not saying that accounts for that age distribution but it probably contributes to it. I just think collecting data from physicians is so problematic because they're so stressed out, they have so many, they're just not, and I wanted to ask Al about that as sort of a second point. Do you find that there's less reporting from physicians now

as the pressure on physicians to see more patients has increased or has it been pretty steady?

DR. DEMARIA: I think there is definitely less but there was never much there to begin with. Basically, we've been depending on laboratory reporting for the last 15 to 20 years. Most of the investigations that are initiated by public health are initiated because of a laboratory report and not a clinician's report. I think that clinicians just assume that somebody is taking care of the rest of the reporting process and that's essentially true. The health department goes to the facility, goes to the practice, says you had somebody who had a positive test for Lyme Disease and somebody in that office gives them information and the provider, the actual clinician isn't involved essentially anymore.

DR. LEIBY:: Okay, I'll make one final comment and then we'll move on. I think the skewing of the rates of infection or at least apparent symptoms being higher in older individuals is interesting because most blood donations go to older individuals as recipients.

So, you might have a convergence of two factors that might impact increased levels of disease in blood recipients that we need to look at. Let's move on to the second question, we did a good job with that one. Does the presence of reservoir hosts for tick-borne agents and persistence of these agents and thereby a greater threat to blood safety compared to that observed from mosquito-borne agents.

DR. SPENCER: Whether it's equal or not, I'd say they both have strong factors mitigating towards persistent in the case of mosquitoes. We know we're not going to eradicate them, any given species from the landscape, that's too hard. But you've got constant sources of travelers and risk for introductions, so I think that the persistence there will endure and in the case of ticks, which are reservoired and invertebrates in nature and the human behaviors we heard of where we settle and where we recreate. I think the factors may be different, but I think they're strong forces that aren't going to go away.

DR. TELFORD: I think part of the issue

with this question is it's almost like apples and oranges, the main driver of transfusion hazard is going to be persistence in the bloodstream, so that when one donates there are infectious particles in that unit.

And so what's more likely to contribute to that is going to be phylogenetic protozoa, babesia seems to persist for a long period of time in the blood and that's -- there's no surprise about that. Chronic infections promote the basis reproduction number from mouse to tick and that's just carrying over into human infection.

But the fact that we have mice around our homes, we have deer around our homes now and at least two maybe three infections that have this well known capacity to cause persistent infection at least in the animal reservoirs suggest the possibility that, yeah, there's more of a reservoir out there.

But the other issue though is that when we talk about arborviral agents and transmission by mosquitoes, we need to separate those which we know are anthropanotic, those that are maintained between humans by mosquitoes, human to human

transmissions or primate to human transmission versus zoonotic, those coming from animals and causing infection and disease in humans. So zika virus and chikungunya equine and yellow fever will never get established in the U.S. because we are very poor anthropanotic reservoirs in this country because we have air conditioning and screened houses and mosquito control.

But we can't protect against the zoonotic infection such as West Nile Virus or Eastern Equine Encephalitis which persists in unknown reservoirs in the forests mainly with birds and bird feeding mosquitoes and episodes where you have the promotion of bridge vectors, human biting mosquitoes that will also feed on birds. And so the two are sort of very different scenarios but I do tend to agree that this large reservoir -- potential reservoir of at least three chronic -- potentially chronic infections in animals around people's homes as a result of tick bites could serve as a hazard for transfusion.

DR. DEMARIA: I grew up in Massachusetts and just sort of observed the

suburbanization which has been remarkable in terms of where people commute from compared to where they used to commute from.

But one thing, when I was an undergraduate I had a job and it's kind of hard for me to believe this now, I had a job collecting mammals for a comparative zoology museum. And the only place we found *peromyscus leucopus* was on Cape Cod, in those days and this was in the '60s.

Maybe it was a little bit of an artifact there, but the only place we consistently brought them back was from the Cape and we went sort of -- we went widely collecting.

But now, I've found -- I live in Melrose just north of Boston, almost walking distance of the city limits and I found a *peromyscus leucopus* in my kitchen one morning.

DR. TELFORD: And, in fact, even though Peter listed *Bartonella* as potentially tick transmitted, it's not. But that doesn't mean that's not something we should be looking for. It is a blood born pathogen, the bacteria reside on the surface or within the membrane -- you know,

underneath the membrane of the red cell and they last forever in the blood of experimental animals in the bloodstream. And everybody has white footed mice in their homes, in their cars, in their kitchens. I trapped two of them from office this last week at Tufts University.

And if you were to smear -- take blood smears from them or culture from their blood 60 to 80 percent of them would have Bartonella in them of a species known to infect humans, yet we don't see this being reported -- you know, no cases are being reported despite the tremendous contact of people with these mice.

We know that this infection is transmitted by fleas between mice, not by flea bite but rather by exposure to excreta containing the Bartonella, just like trench fever is transmitted by body lice and exposure to body louse excreta.

And so that's a big enigma, yet another example of where we have infection all around us but we rarely seem to see it. Some of it is an artifact of not looking, but some of it really relates to infection biology, what is the

susceptibility of primates, including humans, to these infections? And sadly, that kind of question is almost impossible to answer today.

SCID mice, laboratory mice, hamsters, guinea pigs, they're rodents, they are extremely susceptible to these infections and what we see experimentally with those animals may have absolutely nothing to do with primates susceptibility and that's a big gap in research knowledge, is trying to find a way around that.

DR. KRAUSE: I have a question for you, Sam. Is part of the reason that you're not -- one is not seeing more Bartonella infection reported is that the testing for the agent or the species -- I mean, hence lies while there are many labs doing that testing, but these other Bartonella may not -- there may not be laboratory testing available and therefore, you know, it's under diagnosed for that reason.

I just -- I don't know the answer to that. I just wondered what you thought.

DR. DEMARIA: There's certainly somewhat under diagnosis, but like all bacteria there's cross reactivity between the various

Bartonella species. So, serologically, if you have a cat scratch IFA it should pick up antibody to Bartonella Vinsoni. PCR today if you're using a broad range primers against the Bartonellas or Bacterial 16S you should be able to pick it up that way.

So -- and culture, it will grow in blood culture. Cat scratch is one of the more feticides agents, but you know, they say the same thing about Tularemia, yet some people pick it up routinely in chocolate agar.

So I think by now if it was common we would have seen it. And so the big question there becomes, you know, how much attention do we pay to things that are potentially important versus things that we know are important.

DR. LEIBY:: I think that brings us to our next question then. In the face of emergens of multiple tick born agents, was the best approach to identify and then prioritize agents of concerns with respect to blood safety? And I think that's what you're actually speaking to Sam.

DR. TELFORD: We've answered it.

DR. LEIBY:: Well, I think you are in part because we see the issue when you talked about people looking at ticks and then pulling out a whole series of natural flora and that actually, you know, sounds like next generation sequencing sometimes. You know, we're looking for all these things and what do they really mean and are they really a threat to blood safety and do people actually get infected with them? And I think we're going to hear more about that this afternoon.

It looks like Dr. Busch has a burning question for the panel.

DR. BUSCH: The question too sort of -- just to opposing mosquito versus these tick born agents is interesting in that we do a lot of work now, of course, on arbor viruses and one of the key questions there is the role of the tick bite itself or the mosquito bite in mediating transmission, facilitating local expansion of the viral infection and then the immunity that, obviously, once humans are infected we develop antibodies that neutralize infectivity.

So, I'm curious about the relative role

of both the vector transmitting versus transfusion transmission, because, of course, we're concerned about a human who's got an infection and then, you know, transmitting their blood to another person. That may be a very different mechanism of transmission. You don't have the mosquito saliva, you don't have the feces, so it's a -- in terms of minimal infectious dose, both the role of the vector transmission as opposed to parenteral transmission and disease penetrance as well, the probability that an infected person will manifest symptoms seems to be quite different for mosquito mediated versus parenteral.

We see virtually no cases of transfusion dhangy historically or chikungunya, very few cases of zeka, yet humans are getting infected like very frequently and donors of viremic and yet, parenteral transmission doesn't seem to cause anything close to the rate of symptomatic -- either transmission or symptomatic outcomes as do vector transmissions.

DR. TELFORD: That is such an excellent comment and it is a nuance that most people would

pick up on. Here at NIH it's especially apropos because the Godfather of our arthropod salivary pharmacology Jose Ribeiro who is two or three buildings away from us and he's done the most to point out the important co-evolutionary role of the pathogen with ticks and other hematophogous arthropods with the very material that allows them to take blood meals effectively. That ticks have this tremendous immunosuppressive, anti-haemostatic and anti-inflammatory armamentarium in their saliva. Bugs from drugs is what Jose has been working on for a long time and the fact that it modifies the site of the bite to accept -- to promote infection.

And so your comment about, you know, we're missing out on some of this when we're talking about transfusion instances is right on -- spot on.

DR. KRAUSE: I would just comment that -- you know, as I mentioned, there's certainly -- there may be other factors, but certainly three that are important. In terms of question three and maybe this touches a little on your point. And that is the three factors that

one might look at if you're looking at organisms that might get transmitted through blood transfusion would be the amount of organism in the blood, the height of the right bacteremia -- the bacteremia or whatever, the viremia, the duration of that and also how well these organisms survive at blood banking conditions.

So Babesia as an example does well in all three categories. So if you have agents out there in ticks that satisfy those three criteria one would want to look at those especially I would think.

DR. DUMLER: I'd like to add a little to that in contrast to what Sam says and I think the infection biology is everything. There are also instances and rickettsia are a good example of this, where you can use model infections and you can almost uniformly by intravenous inoculation re-establish an infection from the blood of another animal, whereas if you try to inoculate that via tick bite or into the skin just directly, the infection may not take all together.

So there are nuances that involved the

skin, that involve passing the skin, whether it's promoted through a tick bite or preventing it through the skin obstruction and bypassing that, I think there's a lot of research that needs to be done to define those things before we're going to be able to get really useful information out of it.

DR. LEIBY:: Very good. Let's, for the second -- oh, I'm sorry, Dr. Cable.

DR. CABLE: Just in a similar vein to Mike and that -- your comment is Lyme Disease. I took a great interest in finding a case of transfusion transmitted Lyme Disease in 20 years in Connecticut running a blood center. And despite passionate focus on finding one, never did.

I don't think there's one yet or at least not that's come to my attention. There was even a donor who called back after he donated because he developed arithemia -- you know, the rash. We tested the donor, he had both Lyme and babesiosis. He seems to have acquired both Lyme and babesiosis. We went to the recipients, they all got babesiosis and none of them got Lyme from

the same components collected from the same donor at the same time the donor was co-infected. We wrote a little letter on that, that was years ago, you probably haven't read it, but I --

DR. KROUSE: I have.

DR. CABLE: -- suggest you do.

DR. KROUSE: I have.

DR. CABLE: Because it's a natural experiment and so my question is -- well, one theory I always had was maybe because it's being -- the Lyme -- well, we know the Lyme organism grows in blood bank conditions very handedly. It not only survives, it grows. There's a significant viremic phase because it gets all around the body. How long that is is a different question. We don't know that entirely, but it's not causing disease transmission.

Now is that because everybody in Connecticut has got Lyme Disease so you'd never recognize it if it happened? Is it because by being injected intravenously, you don't see the skin rash, which is the only way anybody would ever recognize Lyme Disease? I don't know.

I think rather than -- considering how many germs are in a tick and how much human disease from ticks is growing, I think these issues are much more important for the safety of the blood supply that are coming up now. How -- you know, bite transmission versus intravenous transmission and things that Peter suggested about conditions, I think there's more conditions than we can think about. You just have to differentiate the two kinds of transmissions and yet that's, obviously, why we're here because of blood transmission.

I think there's so little information. And if you don't see Lyme Disease after all this looking, I got news for you, it is not a problem. It clearly is not a problem. And we're not talking about Lyme Disease here and yet we're talking about germs I've never even heard about as being potential hazards. They might be, but I'm -- count me as a skeptic from my experience with Lyme Disease.

DR. KRAUSE: I have two comments. One is I think, you know, there is probably a very brief, although again, if you look at -- I haven't

found answers to the frequency -- or the duration of Bacteremia with Lyme, but I believe it's relatively short. And if you look at the number of cases of dissemination, it's about 10 percent of the cases. This is before therapy was ever developed, it was something on that order. So it's a small fraction of the Lyme cases actually, you know, at least clinically, get into the blood stream. And then when you add to that that most patients are treated, just probably a very small percentage would get into the blood stream.

The second point I'd make is that there's, obviously, you know, there's two ways one could -- maybe there are more, but there are two ways one could think about looking at this issue. One is passive observation and I think you're right, after many, many years if you don't see it it's probably not there. But my guess is if any organism that gets in the blood stream or a number of organisms that aren't shown to be transfusion transmitted probably are in rare instances, so rather than -- I mean, another approach besides passive observation is a prospective study.

And we did a study actually and it wasn't my idea, it was Mike Gerber and Gene Shapiro, but I was brought along for the ride because I did Babesia work. They had a very ingenious way of doing this, which was to look at patients undergoing cardiac surgery who receive many transfusions and so in consecutive patients, I think it was six or 700, there was an attempt to look at the presence of transfusion transmitted Lyme and Babesiosis. And in that case, I think out of the 600 there were like -- there was one case of Babesiosis and none of Lyme and so I'm saying that concept is really good. I think the weakness of that study was, we didn't have enough money to lots and lots of patients, but that is one idea to think about if you -- to look for this, is you do some kind of prospective study like that. Sort of active surveillance as opposed to passive.

DR. TELFORD: Just as a brief comment on the Lyme Disease, which were not supposed to be talking about and there are good reasons for that. It's not a hazard, but it is not correct that it's not in the blood. Gary Wormser

published a study ten years ago or more showing that if you take acute Lyme Disease patients presenting with arithemia migrants or arithemia illness and you put 20 mls of blood, whole blood into 100 mls of BSK cultured medium the sensitivity is 65, 70 percent of the time you will grow spirochetes out of that.

And similarly I happen to know some data where -- which we're going to be publish, which suggests that you can do the same thing with PCR. 60, 70 percent of the time, a person presenting with acute Lyme Disease will have borrelia burgdorferi DNA in their blood.

And so it's clearly in the blood at a frequency sufficient to expect to see some transfusion cases. And I think the comment about tick saliva is absolutely correct, that the spirochete is inoculated in very small doses into the skin and the site of the bite is prepared by the salivary products and that is important for initiating the infection process.

And whether these other agents require that as well Steve may want to comment about an aplasma and maybe the attraction of neutrophils

to the site of the tick bite as promoting infection, but we need to know more of these basic biology questions.

DR. LEIBY:: I think I'm going to jump in here, because we're coming up against the time stop. You guys could go on forever and everyone will miss lunch and then people would be very unhappy.

I think question four was on climate change. I think we had just touched upon that, it wasn't really a topic for today, although Sam certainly said that maybe the ticks would be moving north and they'll have problems up there. And I think in light of a lot of the discussion we've actually answered question five about what actions need to be taken and what we need to look at.

So I think in that sense I think we'll shut down the discussion now so that we can all get some lunch and be back here promptly at 1:20.

And I'm sure any of the speakers will be happy to talk to you at lunch or at the break if you have some more tick borne questions. But thanks to everyone and thanks to the speakers.

(Recess)

DR. LEIBY:: As you can tell, I like to stay on time. Let's wait for a couple stragglers to come in here.

In the meantime you have the privilege of hearing from me once again. This time I'm actually speaking, so I'll actually introduce myself. I'm David Leiby from FDA CBER. I did my undergraduate work at Lafayette College in Easton, Pennsylvania, Masters from Rutgers, Ph.D. from the Ohio State University. I did my post-doctoral work in cellular immunology at the Walter Reed Army Institute of Research nearby here. Worked at the Red Cross for 21 plus years and have been at the FDA for the past two.

And what I'm going to speak to you now is about transmission risk opposed by emerging agents and I think this will kind of set the -- what's a preface for what we're going to talk about for the remainder of the afternoon.

And I think it's important to talk briefly about what kind of agents we actually screen blood for. At this point, you know, these are all tranfusable transmissible agents and is

a fairly long list.

We test for HIV I and II, HTLV I and II, hepatitis b virus, hepatitis c virus, treponema palladium, syphilis, west nile virus, trypanosome cruzi, t-cruzi we just test each donor once. We test for CMV cidomeglar virus and as the asterisk indicates, that's testing done under -- well, it's negative units, a group of blood units are tested to make negative units, which are then provided to at risk recipients.

And the last two, babesia microti and zeka virus are tested under IND, babesia only in selected areas at this point and zeka virus is now under nationwide IND testing.

You know, the question is how do we get there? How do we determine who's at risk and how do we get to testing certain agents?

We've seen facsimiles of this or discussions throughout the day, but how do you get to transfusion transmission or transfusion transmissible agent? Well, there's a number of factors that actually have to occur.

First of all, a donor has to have an active infection. By active I mean, it's on

where the infection is ongoing, it's not one that's cleared by the immune response. They actually have to have something going on inside them.

Probably most importantly is the agent has to be in the peripheral blood. I think as we heard earlier today from Steven Dumler, if you don't have the agent peripheral blood, which often happens with Rocky Mountain Spotted Fever you're not likely to get transmission cases. So the agent has to be in peripheral blood for at least a significant portion of time. And I think that was a nice point by Peter Krouse this morning, it has to be -- transmissible agents are likely to be the ones that are in peripheral blood and are there for quite awhile.

Importantly, the agent, once it's collected comes from peripheral blood has to be able to survive the collection process and storage. And there are different collection processes as well as different storage lengths depending on what kind of product it is.

And lastly, once it survives all these things, the agent has to be able to establish an

infection and blood recipient.

What I want to do for my talk this afternoon is talk about each of these and how they actually relate to being at risk for infection.

And we'll start with the idea of blood donors getting active infection and I'd like to go to the concept of adding emergent infections. And we talked about this quite a bit this morning, so I won't spend much time.

This list actually comes from -- it's getting rather ancient now, but I still think it's good, the Institute of Medicine Report from 1992 on emerging infections, microbial threats in the United States. And this had a list of seven factors which influence emergens. The last three I don't think are of much consequence for ticks, international travel and commerce, poverty and social inequality and war and famine. At least as we speak to the U.S., it may have implications for other parts of the world.

It's actually these four which we've talked about quite a bit, climate and weather, changing ecosystems, human demographics and behavior and lastly, economic development and

land use all tie into emergence of tick borne diseases.

I had this kind of collage slide, but I think we've talked about all these things earlier today. The topics of reforestation, the moving of suburbia into the areas where the forests are, where the deer and the mice live, the fact that the temperatures appear to be going up worldwide and we seem to be spending more time in those kind of environments where it might be exposed. But I won't belabor that, because we heard that this morning.

I also won't talk about active tick borne infections, these are CDC reports from 2014 for babesiosis, anaplasmosis, ehrlichiosis and for spotted fever, just the regions where they had case reports. Again, the concepts of these agents emerging and spreading across the country and certainly we see more and more of this.

Now, getting to something new though and I think this is relevant is, we said the agent has to be in peripheral blood in order to be transmitted by blood transfusion. And, in fact, most of these tick borne agents are ready to go,

they all have intracellular niches or many of them have intracellular niches within blood cells.

We talked quite a bit about *Babesia microti* being in erythrocytes. This is a nice picture of aquidine orange of *Babesia* inside red cells.

Ehrlichia chaffeensis infects monocytes.

Anaplasma phagocytophilum and *Ehrlichia ewingii* inside granulocytes, all those are blood cells which we routinely see. So they would be easily transmitted by transfusion if they are present.

In contrast, there are some that are cell associated like *Rickettsia*, I even found it in endothelial cells. Those aren't as likely to be transfused or not as readily as these guys up here.

We have to also acknowledge that sometimes some of these agents are free and extracellular, which then brings in the role of plasma and sera. There are cases where you see *Babesia microti* as well as *Ehrlichia chaffeensis* free in plasma or serum extracellular nature, so that must be a concern as well.

What about blood product processing and storage? Certainly there's collection

processes, sometimes we collect whole blood, sometimes a aphaeresis. There are leukoreduction, I think, on the order of about 95 percent of the blood in the U.S. is leukoreduced, I think that's still accurate.

Leukoreduction can be done either in process, in other words by aphaeresis or by active filtration to remove leucocytes. And this is largely done to reduce the risk of sidomaglavirus transmission.

Some blood products are also radiated and that's used for patients who are at risk for transfusion associated graph, which is host disease, selected immuno compromised patients, so that's important as well.

Lou Katz will speak to this mode later, but some blood products are also pathogen reduced. There are some licensed products out there for pathogen reduction and this helps to reduce and eliminate transfusion transmitted diseases and it also has an added feature of potentially obviating the need for radiation, the one right above that.

And lastly, storage conditions can have

a certain impact upon the survival of the tick borne agents and that varies by products.

And what I'm going to do is spend my time on leukoreduction and storage conditions giving you some examples and some of the past literature and how this all might work together.

The first mention of leukoreduction in papers that I came across was this paper on Survival of Ehrlichia Chaffeensis and refrigerated ADSOL treated red cells and this is from 2000 by Don McKechnie.

It didn't directly look at leukoreduction or look at the effect of filters, but what it did was it -- it made an implication based on some of the study results and what they did was they took ehrlichia chaffeensis was isolated from a supernate infraction and so based on the time required for detection of e chaffeensis in culture they had both pellets and supernates and they grew these out in culture and they can tell whether or not the parasite was able to survive.

And what they noticed was that it would survive quite well in the pellets up through about

11 days, but it wasn't present in the supernate through five. And so what they did, they drew an implication that leukoreduced products would still contain the agent because it was present in the plasma.

Now to look at this issue more directly this is a paper by Melanie Proctor at the Red Cross and myself and as to leukoreduction filter is passively reduced the transmission risk of human granulocytic anaplasmosis. This was published a couple of years ago.

And in a study, Melanie took some blood units infected them with anaplasma, they were leukoreduced, separated the plasma and leukoreduced red cells, used three different infection levels and then monitored the ability of the parasite -- or not the parasite, bacterium to grow inside self cultured systems. And it did three replicates of each and different -- three components, three replicates.

Now what was obvious in all positive controls, all of them grew out anaplasma. If you look at plasma you see at some lower levels after being -- there was some difference in the plasma

levels, a couple of them grew, some of them did not. But the one important one was a leukoreduced red blood cells in which none of the leukoreduced at this lower infection level.01 percent grew out anaplasma. A few more appeared at 1 percent and still the same kind of factor at 5 percent where some were removed and some were not. These are just some cell culture pictures with the parasite inside.

What this means summarizing is that leukoreduction filters do remove some of the anaplasma agents but not all the anaplasma agents. So leukoreduction is not the panacea for eliminating transfusion transmitted anaplasmosis. And actually there have been several reports of TTA implicated looking at leukoreduced red blood cells and I don't know if Sue might talk about that more in her next talk.

What about blood component storage? Blood components are stored under a variety of storage conditions and have different expiration dates dependent upon what they're stored in and what they're used for. Red cells generally store between one to six. There's a variety of

different solutions. They're stored in an additive solution, they're kept for up to 42 days. That's what we commonly think of for the shelf life of a red cell unit.

Frozen red cells can be stored in 40 percent glycerol. These can be stored for up to ten years, perhaps even longer and they're stored at -65 degrees C. Platelets, a rather short shelf life of only five days, 20 to 24 percent -- 20 to 24 degrees with continuous agitation. Fresh and frozen plasma anywhere from 12 months to 7 years depending on the temperature that they're stored at. Liquid plasma, a very short shelf life, five days and that's kept at 1 to 6 degrees.

And then, lastly, and I'll come back to this later, aphaeresis granulocytes are only stored for 24 hours or less and those are stored at 20 to 24 degrees.

Now what I did is I went through the literature that I had available that I could find and looked at a number of these agents and what kind of studies were actually done to characterize their ability to survive in what

storage conditions.

Beginning with b microti and Mark Eberhard when he was at the CDC did a study way back in 1995 in which he took infected red cells that were maintained in EDTA tubes. Not the best because, you know, they're maintained in glass tubes, there's no ability to breathe and survive very well. But he was able to show was that the babesia survived at four degrees for 21 days and at 25 degrees for three days.

Now, Stephanie Johnson and her colleagues at the Red Cross published a paper in transfusion in 2012 and this was actually studied looking at look back for b microti in Connecticut. And as part of the look back investigations, they found a case implicating a 42 day old red cell unit. So that implies that the parasite can survive in a red cell unit for the entire shelf life, 42 days.

Annals Internal Medicine paper in 1982 described a transfusion case due to cryopreserved red cells and that was by Grabowski et al. So what we see for b microti, it survives for the entire shelf life, it can survive in a

cryopreserved red cells, so it's something that appears to have survived quite well and should be a concern.

There's fewer studies for the rest of these agents, for anaplasma phagocytophilum. Kalantarpour in 2000 published a paper where he actually took infected patient blood specimens, so actually individuals who were infected with anaplasma, collected their blood, maintained them at four degrees and tried to measure how long the agent survived and the agent actually remained viable for up to 18 days, so, apparently, quite well.

The first transfusion case of anaplasma described by Ted Easeland in 1999 and this case implicated 40 day old red cells.

And, lastly, Rebecca Townsend, from the Red Cross and colleagues published a case in 2014, this was a transfusion case involving a five day old aphaeresis platelet unit.

So, again, we see that the organism survived quite well, whether it's in aphaeresis platelets or it's in red cells. So the agent anaplasma seems to fulfill that requirement to be

able to survive storage.

Fewer studies for monocytic ehrlichiosis or ehrlichia chaffeensis, McKechnie in 2000 Infected Monocytes as I earlier said in ADSOL and then look for survival and as I said, they survived for 11 days at 4 to 6 degrees. And then a study which Peter Krause mentioned earlier where Thorpe and Tonnetti from the Red Cross looked at borrelia miyamotoi and this was published just last year, survived red cell storage for -- at

degrees for 42 days, again, the complete shelf life of the red cells and also survived platelet storage at 24 for five days.

It was killed, apparently, when it was put in plasma stored frozen, but as far as red cells and platelets storage, it survives for the entire shelf life. So taken together these agents appear to be able to survive blood storage conditions quite well.

So once they get collected, once they're in peripheral blood, once they've survived storage they have to get into the patient and actually replicate and cause disease.

So I wanted to spend a little time considering or looking at risk in recipients. Who's at risk for becoming infected and actually becoming potentially ill.

The first group I'll mention is the immunocompetent recipients and while they may be less at risk because they're immunocompetent, any immunocompetent individual is at risk for infection for a transfusion transmitted agent, so we must consider them to be at risk.

More at risk are immunocompromised recipients, all be it they are difficult to define if you want to talk about immunocompromise, but they do include individuals with a variety of medical conditions, those who are elderly. I think Peter Krause is still here. I remember years ago, Peter was asked to define the fact that babesia patients are more at risk -- individuals are more at risk for acquiring babesiosis when they're elderly. When asked what elderly meant Peter said, 50 years or older. So I think many of us fall into that category and if you're not 50, you have something to look forward to.

Immunocompromise recipients

particularly babesia also include asplenic and functionally asplenic patients who necessarily aren't more at risk but they have more severe disease when they become infected of babesiosis.

Probably by definition multiply transfused patients are more at risk. They receive more blood products and that may be because they're trauma patients and they receive large boluses, lots of blood products at the time of whatever trauma it might be. But there's also a group of chronically transfused recipients for medical reasons who on routine basis go and get blood transfusions and those individuals are at greater risk as well.

As we've seen today there's also a geographic risk, so exposures to vectors and/or agents. So, clearly, the people living in the northeast have greater exposure to a lot of these ticks and maybe have greater risk for tick borne infections.

Individuals living in Florida, the gulf coast might be more at risk for arboviruses and mosquito borne transmissions. There's also seasonal exposure risks. We've seen that now, I

think, in three or four of these tick borne agents today, they have almost identical curves as far as exposure and having infections June, July and August, seems to be those periods when they're at greatest risks, with some exposures in October as well.

I mentioned granulocytic transfusions, well the granulocytes only have a shelf life of one day, but they're also often transfused to patients prior to the receipt of test results. So one could receive an infected unit without knowing it because it hasn't been tested yet.

Another risk which has to be taken into account is actually the absence of effective interventions. If we have no interventions for some of these agents, then they are by definition at risk as well.

So one good look at this list and maybe it's cumulative, but over time some of these recipients they may be immunocompromised, they may at the same time be multiply transfused, they may live in the northeast and they maybe seasonally exposed, so they have a greater risk than others. But the concept here is recipients

have a multiple factors that lead to them be at greater risk.

And the last slide and this is actually a nice slide to lead into Sue's talk and this is the end result of all those things I've talked about, transfusion, transmission and active infections. Well, we know there are active infections because there are all kinds of transfusion and transmitted tick borne diseases.

This paper that was referred to earlier by Barbara Hurlwaldt on transfusion associated babesiosis, a case of Colorado Tick Fever in Montana in 1975, ehrlichia ewingii acquired through platelet transfusion and transfusion transmitted in a plasmosis in a leukoreduced platelet pool. So each of those agents also play a role in transfusion transmission and that's just the short list.

So in summary then, tick borne agents do pose a risk for transfusion transmission. The agents as we've shown produced active sometimes asymptomatic infections and that also came up this morning that those who are asymptomatic are the ones we probably have to worry about the most,

because they're the ones who will say they feel fine when donating blood but they are actively infected.

Many tick borne agents reside intracellularly in peripheral blood cells and as I've shown you in a short number of slides, they survive quite well in those blood cells and they also seem to survive leukoreduction.

And, lastly, there's evidence for establishments of infection and blood recipients, which equates to transfusion transmission and so that's something that I think Sue will talk about as well as others this afternoon.

And I think it's my duty to give you one more tick cartoon humor, so this is a recent "Speed Bump" by Dave Coverly. It says, here comes Ron whatever you do, don't mention the dog and the tweezers.

For any of you who have dogs and you have ticks, you know all too well about the dogs and the tweezers.

But anyway, thank you very much and I'm happy to entertain a few questions.

DR. KLEINMAN: Hi, David. Steve Kleinman from AABB. Do you think the explanation for the -- in going to leukoreduction and anaplasma, do you think the reason for the failure of leukoreduction to protect is that you just can't get at every last infected granulocyte? Or is there a free -- or do you think it's the organism in plasma?

DR. LEIBY:: I would suspect that it's probably both of those. I think the leukoreduction filters aren't 100 percent, someone correct me if I'm wrong.

DR. KLEINMAN: No, you're not.

DR. LEIBY:: But I think there's also some extracellular agents, certainly when the cells burst and reinfect other cells, I mean, there are going to be free agents. So I think we just can't get everything with the leukoreduction filter.

And that's been shown by other studies too. There's been studies with *t. cruzi*, for instance, attempts at leukoreduction and by and large they always seem to reduce infections, they never seem to eliminate them entirely.

DR. KRAUSE: Hi Dave. Just wanted to comment on the age 50 issue. People at 50 are young. No --

DR. LEIBY:: Did you make the previous statement when you were 48?

DR. KRAUSE: I think, you know, there's a continuum and older people do have immune -- some immune impairment and as you get older I think it gets worse, but there isn't any strict cutoff so to speak and it may be somewhat arbitrary and there's not a lot of data and it may be that future studies will show that really 50 and 40 are not a lot different, but

you start to get more -- so there is some data, I'm just saying it's not airtight let's say.

DR. LEIBY:: So 60 is the new 50; is that what you're saying?

DR. KRAUSE: Yeah, I would agree with that.

DR. LEIBY:: Okay.

DR. KRAUSE: Okay. Thank you.

DR. LEIBY:: Thanks, Peter. Okay.

If there's no other questions we'll move on

to our next presentation. The next

presentation is by Sue Stamer and she's the Vice President of Scientific Affairs and Biomedical Services at the American Red Cross where she's been for the past 21 years.

Her primary interests are infectious disease of blood, epidemiology interventions. She's a past president of AABB and currently is the chair of the Transfusion and Transmitted Disease Committee of AABB. I think she went to Wisconsin and she spent time at Abbott, so we'll stop there.

DR. STAMER: Thank you, David. Thank you all for coming back from lunch, that delicious lunch.

Anyway. So my title -- the title that was given to me is Incidents of Transfusion Transmitted Human Granulocytic Anaplasmosis, TTHGA, which is caused by anaplasma phagocytophilum and I've included other tick borne agents.

Okay. I do have some conflicts to declare. I really won't be talking about any of these in this presentation.

So my outline today is to describe tick

borne agents that include viruses, rickettsia, other bacteria because, of course, rickettsia are bacteria and protozoan parasites that are or have the potential to be transfusion transmitted.

So I'll provide some detail for interesting agents, provide detail for TTHGA cases, that was what I was asked to cover and I'll touch very briefly on pathogen inactivation since Lou will probably cover that after myself.

So in order to answer some of the questions that were posed this morning and it's always a good baseline to talk about what's required for transfusion transmission, David did cover that nicely in his talk, but let's answer the question that has been posed by many and answered actually in a chapter that Roger had published that I cite here.

So the question we're trying to ask is what constitutes transfusion transmission and when is that agent of concern? So how do we answer those questions?

First of all, you need to identify an agent and as David and others have already mentioned today, that requires an asymptomatic

blood borne phase, the agent must survive or persist in the component during preparation and storage, the agent must be a pathogen, it must cause disease and that disease must be manifested in blood recipients.

So the disease may vary in severity, mortality or treatability in those only to be considered. Immunosuppression as we've talked about, favors more severe disease.

So some other factors that influence the agents, influence are donor prevalence and the prevalence is the agent present in our donors? Is the prevalence increasing or is it declining?

Another important aspect that may not be on the scientific matrix, but certainly is the public concern matrix and what is public concern about the agent? And, of course, for these agents, many of them our public has never heard of and many of them, of course, they're very familiar with.

So once we have all of these questions answered, are there effective interventions for elimination or reduction of those transfusion transmitted agents?

So this is a collage, everyone has to show pictures of ticks. So these are the ones I put together. David already referenced tick on a bagel. So you can see the size of a tick on the poppy seed bagel, you'll probably never eat a poppy seed bagel the same way again.

You can see right smack in the middle, these are all pictures of ixodes scapularis, a nice engorged tick. The range shown on one of the top slides and the obligatory tick on a coin, so the tick is crossing the word trust on the penny.

So what I have done and used the prior flow diagram of the questions we answer regarding the severity and in trust transfusion transmission is a group of us at AABB put together fact sheets describing agents that are or have the potential to be transfusion transmitted. They were published in transfusion in 2009, many of the fact sheets were updated.

So what I did is went through all of the fact sheets to pull out those agents that are tick borne and to give you some salient features about each of those agents. I apologize in advance, I forgot Tularemia, but perhaps no one will have

noticed that if I didn't say so and then I added a couple of agents.

So starting with viruses, we have Colorado Tick Fever Virus and if there's a red asterisk after the name of the agent it is because there has been at least one documented case of transfusion transmission. So Colorado Tick Fever is a real virus, it's double stranded RNA, unenveloped, a resistance verocal virus. The vector is the adult rocky mountain wood tick. It's distributed in the Rockies, the Sierra Nevada Ranges and other locations in the western U.S. It's Intraerythrocytic, it causes a flu like illness with a rash, 20 percent of patients are hospitalized and they have prolonged viremia.

And there's been one TTI case, transfusion transmitted case from an eight day old unit of whole blood in 1975, so really nothing very recent.

Then we go to Crimean Congo Hemorrhagic Fever Virus. This is a bunyaviridae single stranded RNA enveloped spiracle virus, it's vector are Ixodes ticks, including hyloma and others. It covers the greatest geographic range

of any tick borne agent. It's reservoir is livestock. It has a rapid onset of a wide variety of symptoms leading up to hemorrhagic fever at about five days after the onset of symptoms. It's classified by the CDC as a high priority bioterrorism threat agent. It's mortality is 10 to 50 percent and it's never been associated with a transfusion case, however, there is a viremic phase, so it is possible or theoretical as we said.

Then we move to the tick borne encephalitis virus complex agents and there has been transfusion transmission. This includes TBEV, the name of the group, tick borne encephalitis virus and powassan which has already been mentioned and it's close relative deer tick virus as well as others.

These are flaviviridae, they have single stranded RNA, they're enveloped spherical viruses. TBE occurs in Eurasia and China with powassan and deer tick virus occur in the northeastern U.S., north central U.S. and southern Canada and that's dissimilar to babesia. The vectors are ixodes ticks and others including

dermocenter. The reservoir are small vertebrae hosts and they have a woodchuck, weasel or mink, otter cycle.

In order to get infected with powassan it's really rare, you have to be very close to where these burrows of these animals complete their lifecycle. And it's said and we said it in the fact sheet, that multiple generations of ticks infect single animal, so it's really unlikely for humans to be in contact with this agent.

For TBE the reservoir is livestock. Transmission can also occur for TBE via unpasteurized milk. Its seroprevalence in Europe for TBE is up to 28 percent, up to about 6 percent for powassan and that was documented in Ontario. Powassan is actually a city in Ontario where the virus was first isolated.

So from viremia you can develop flu like illness including encephalitis which occurs and may be severe in up to

percent of those who develop clinical syndrome. There's been one TTI case of TBEV and that occurred

in Finland in two recipients who received blood from the same infected donor and the two recipients and the donor were linked together because they were sero positive. There was no other genetic linkage or anything like that.

So the agents that I've added here as far as tick borne viruses include Heartland, Bourbon and severe fever with thrombocytopenia syndrome virus. These are all probably -- these are all very closely related viruses, they're bunyaviridae all in the phlebovirusgenus, they're single stranded RNA enveloped spherical viruses. The vector for Heartland and Bourbon is *amblioma americanum* and for SFTS it's *hemophasalis longicornis*, well you say it, anyway. And that's the one in China.

So in 2009 Heartland was first identified in Missouri in two farmers who simultaneously presented with fever, fatigue, diarrhea, thrombocemia, thrombocytopenia and leucopenia, even though these two farmers lived 60 miles apart from one another it was serendipitous that they should have presented at

the same time.

Since those two cases, there have been eight total cases reported in Missouri and Tennessee and CDC has been actively following on the movement of Heartland.

They've also identified another agent called Bourbon, which was identified in 2014 in Bourbon County, Kansas. This was a fatal case. The presentation was very similar to above.

And then in 2011 SFTS was identified in China, again, with a similar clinical presentation and to cite the first publication in New England, we isolated a novel virus designated SFTS bunyavirus from patients who presented with fever, thrombocytopenia, leukocytopenia and multi organ dysfunction. RNA sequence analysis revealed that the virus was a newly identified member of the genus phlebovirus in the bunyaviridae family.

EM examination revealed variance with the more phelagic characteristics of a bunyavirus. The presence of the virus was confirmed in a 171 patients with SFTS from six provinces by detection of viral RNA, specific

antibodies to the virus, blood or both.

Serologic assays showed virus specific immune response in all three five pairs of serum samples. So, clearly, a new agent.

So now let's move to the rickettsia. Rickettsia R bacteria, they're defined as gramnegative obligate intracellular arthropod borne bacteria.

So the first one is ehrlichia chaffeensis. The agent of human monocytic ehrlichiosis. The vector is amblyomma americanum. The Lone Star tick and Dermacentor variabilis and also Ixodes species can be involved. The reservoir is the white tailed deer. It's present in 47 U.S. states in south central and southeastern United States. The most recent claim to fame of this agent was from a military blood drive in Fort Chassis, Texas that occurred after an extensive exposure to ticks. The donors developed febrile illness, 377 who were seropositives were identified who were infected or seropositive for ehrlichia chaffeensis and rickettsia rickettsii, which is the agent of Rocky Mountain Spotted Fever. And

no transfusion transmissions were documented from ten trace recipients from these positive donors.

The seroprevalence of the agent is 3.6 percent. It survives in monocytes for at least 11 days with organisms present in the supernatant. It can be severe, hospitalization has been reported in greater than 40 percent of the cases with respiratory and renal failure, menogial encephalitis and GI bleeding.

So another species of ehrlichia that I want to highlight will be ewingii, but first generally about other species of ehrilichia, they infect granulocytes, not necessarily not all monocytes as chaffeensis. There's a emerisis like agent that's been described in Wisconsin and Minnesota. The vector is amblioma or germocentor possibly ixodes. The reservoir is dogs for ewingii and there is a asymptomatic bacterimia for probably greater than three weeks. And as mentioned by David, there is one transfusion transmitted case that has been published and it's the first case of transfusion transmission for an ehrlichia species. It was

linked to transfusion of five day old platelets that were leukoreduced and irradiated. The recipient was a nine year old with ALL in Georgia, the recipient had no other risk factors and clusters of organisms, that is, thrombulae were identified in granulocytes in day 11 after symptom onset. The patient was treated and recovered.

The bacterium, the rickettsia was identified by PCR and sequenced. The donor remained asymptomatic but reported tick bites in wooded areas in his homes in Florida and South Carolina and was antibody positive.

The next rickettsia is rickettsia rickettsii, the agent of Rocky Mountain Spotted Fever. It has -- it's been associated with a transfusion transmission that I'll mention. It's endemic in the western hemisphere throughout the western hemisphere. The vector is Dermacentor species and others. The reservoir are ticks where the ticks for this agent complete their lifecycle within ticks, so they don't necessarily need another mammal to participate in their lifecycle, but also rodents and dogs may be

infected.

It's been classified at CDC as a moderate priority bioterrorism agent. It is high mortality in untreated patients and antibodies develop only after the onset of disease and the one TTI case was a nine day old blood, the donor developed Rocky Mountain Spotted Fever three days after he reported post-donation information. The donor died, but the recipient was treated and did recover.

So next we'll talk about anaplasma phagocytophilum which has been, of course, transfusion transmitted, it's the cause of HGA, which the organism lives in granulocytes specifically in neutrophils. The vectors is ixodes scapularis in the northeast and north central U.S. and pacificus in the western U.S. and ricinus in Europe. The reservoir is the white footed mice and small mammals.

You get disease seven to ten days after the tick bite which starts as a bacteremia and then develops into acute symptoms. There's up to 15 percent prevalence, which has already been mentioned in Wisconsin, Connecticut and New York.

In one study there has been a higher prevalence reported in New York. Risk patients are the elderly and immunocompromised with less than a 1 percent mortality rate.

Now the 50 years for the definition of elderly actually I had first seen from the CDC, so I think if we're going to talk about who defined 50 as the new 60 or however we want to phrase that, the definition of elderly at over 50 comes from the CDC.

So for anaplasma there have been 10 TTI cases reported in the United States and I'll give you a review of those. Two are from non-leukoreduced red cells and that was before leukoreduction was used and five were from leukoreduced red cells, including irradiated red cells and they were up to

days old, one of them at least, the Eastlund case as David mentioned, was up to 30 days old. Two leukoreduced platelets or platelet pool and those were either four or five days old and for one out of the ten components age was not provided.

So for anaplasma, I have three slides

that I included or three pictures in this slide. One is the distribution of anaplasmosis reported by the CDC and then increasing frequency over time and the distribution of cases by year. So, clearly, in July -- June, July and August, the highest numbers of cases. It's nationally notifiable since 1999. It's distribution is similar to Lyme. It can easily be misdiagnosed as ehrlichiosis, so there could be under or over reporting. It's increasing in frequency, it's present year round but most frequently during the tick season, same distribution as *B. microti* and it's increasing frequency with age and likely due to greater tick exposure or perhaps greater susceptibility with age.

So here are the ten cases, across the top row is the year, the location of the case, all of them in high risk areas, in the upper mid-west or New England area, with the exception of one in Slovenia. There's nothing dramatic about the age distribution or the sex of the recipient or even the underlying condition. Any underlying condition has been associated with these ten cases or a wide variety of underlying conditions.

So in red on the third line here, I've given you the age of the components 30 days or whatever the days here are for the leukoreduced red cells and then these are the two from platelets four and five days old. And you have the diagnosis here and then the common denominator here is they were all diagnosed by PCR. Most of them were diagnosed by smear, some were diagnosed by serology. The implicated donor and how they were diagnosed is provided in this row, but what I highlighted in red was underlying risk factors, they were Lyme positive, they had reported tick bites, they were a hunter, more tick bites, tick bites or they were associated with a donor who later developed HGA.

So, David, already showed the slide with a picture of -- this is a cell culture line and you can see morulae in the cell culture slide, here is a blood smear, again, with a nutrifill and you can see the agent there in the microcolony.

So this paper now, I think this is the third time it's been referenced today, but what happened was whole blood was spiked with antiplasma, three concentrations, blood was held

to 24 hours and then processed into red cells and plasma and red cells were leukoreduced. So the negative control is mentioned, had no positives in triplicate testing, the positive control was positive 100 percent of the time. After

hours prior to leukoreduction all were positive at all three concentrations. Plasma was sporadically positive at the lowest concentration but consistently positive at the higher concentrations and leukoreduction was sporadically effective at the lowest concentration it was, but at the higher concentrations it was not, with four out of nine or five out of nine positive breakthroughs.

So now we're going to move on to other bacteria which includes spirochetes. So the first one is borrelia burgdoferi, it's the agent of Lyme Disease, which is the most common vector borne disease reported in the U.S. So I said greater than 20,000 cases, greater than 30,000 cases, greater than 300,000 cases, it depends what data you believe. It's common just like babesia and anaplasma in the northeast and north central U.S. The vector is the same, ixodes

scapularis in New England or the north central U.S. and pacificus in California. The reservoir, again, is the same, white footed mice and deer serve as a transport vector although they're not infected. The tick requires attachment for infection for at least 36 hours. Probably as discussed this morning there's some variability around that number. It survives in fresh/frozen plasma, red cells platelets for the duration of storage. There have been no TTI cases reported despite look back from DNA positive donors and, again, something that was discussed extensively this morning.

And so I will then tell you about babesia miyamotoi and I will close with babesia.

So for borrelia miyamotoi, a lot has been published on this newly identified agent. It's the cause of relapsing fever, it's the relapsing fever spirochete. It was first isolated from ticks in Japan in 1994. For human disease it's the same tick vector as borrelia burgdorferi. It's been reported to be in high titers in blood versus lower titers for burgdorferi.

So, again, this one is probably a greater risk for transfusion transmission than burgdorferi, again, because it's present in much higher titers and blood.

The 46 human clinical cases that were identified in Russia in 2011, 10 percent with relapsing fever, another 18 antibody positive cases, three with clinical disease in the northeast U.S., most from a population of confirmed or suspected Lyme Disease patients. Meningoencephalitis has been reported in several patients. It also can be identified from cases presenting at HGA or other tick borne agents, including Lyme Disease. And, lastly, the sero prevalence in New England has been reported at about 5 percent.

So, again, this study was presented earlier today. Aaron Thorpe and Lauren Tonnetti looked at the distribution and survival of borrelia miyamotoi and this was really a follow-up study to that described by Peter Krause earlier this morning about survival of the agent in mouse blood for seven days and its ability to be transfusion transmitted in a mouse system.

So what Laura did actually in this study, was take the agent spike human blood, hold human blood for a period of time and then reiterate it in mice or reiterate it in an invitro system. Well, in the mouse system whether it was wild type or immunocompromised mice, there were differences.

So the wild type mice were able to clear virus after -- clear borrelia after 42 days, but in plasma after it was frozen there was no recovery and in platelets the agent was still present. So but in SCID mice there were no ability, at least in red cells, regardless of age, for these mice to clear infection, so in an immunocompromised host this is probably much more significant, again, platelets all were positive.

So in the invitro system and sub-cultural this time leukoreduction was investigated at two concentrations, a high concentration and a lower concentration, leukoreduction was differentially effective at the lower concentration it was, but not at the higher concentration.

So here you see some pictures of the

spirochetes. Here's Lyme and here are two from Laura's publication, dark field with equidine orange or in a blood smear, so you can, clearly, see the spirochetes.

So lastly, a few words about babesia. It's an intra erythrocytic tick borne parasite. It's the -- at least *B. microti* is the most frequent cause of tick borne fatalities reported to the FDA. In the study by Hurwath that's been referenced earlier today, there were 162 cases reported to CDC. The vast majority being *B. microti*, but a smaller number being *B. duncani*, which on this map is present on the west coast. *B. microti* is present in nine endemic states, it's now required to be reported or it's nationally notifiable. Not all states, as mentioned earlier today, report, but 99 percent of cases do come from nine states.

I show this map also because there are other species, not just *B. microti*. I also mentioned *B. duncani*, but there's *B. divergens* and MO1 in the center of the United States and that's relevant in a subsequent slide that I will show.

But outside of the United States

babesia certainly has been reported and documented. There are over 100 species of babesia. There are 39 clinical cases have been published in Europe, mostly from divergens and venatorum, but also from microti. There are variants that have been described in Asia, KO1, a Taiwanese strain. There's been one transfusion transmission in Japan from a b microti like organism that they call a Kobe strain, which, obviously was recovered in Kobe in Japan. Canada had one transfusion transmission, it actually occurred before the first documented clinical case of babesia microti in Canada, but it was published subsequently. And as Al said this morning, when was the last time you went to Cape Cod? So this was a donor who did travel to Cape Cod.

I mentioned divergens like MO1 strain, so there was one possible TTB divergens like MO1 transfusion transmission that was published in CID this year. It's questionable whether this is really a transfusion transmission. The title does suggest it's possible. It occurred in an 81 year old asplenic male who had a significant

medical history. He received actually seven red blood cells from five donors in Arkansas and Missouri, developed severe anemia, he was diagnosed on a smear two to three months after receipt of the donations. There was no blood donation tracing, no tick exposure, he was PCR positive for MO1 and PCR negative and antibody negative for a variety of other agents. So in total this was the 5th case of an MO1 like strain documented in the United States and the first possible TTI.

So this shows you some photographs of babesia, this is in hamster blood and here you can see multiple babesia organisms infecting a single red cell and this is relevant for the next slide that I will show you. Here's the Maltese cross, it's diagnostic of b microti and then this came out of the paper from the MO1 divergens transfusion transmission.

This patient had 10 percent parasitemia, so it was, obviously, easy to see things in a blood smear. Seroprevalence, there was also an agent that was identified and here are multiple ring forms, again, similar to what I

showed you in hamster blood.

So, lastly, I will tell you, at least, for babesia as well as true for many of these agents, they're very susceptible to pathogen reduction technologies. In this case it's the cerus technology which is being used under research in clinical trials and in this case, Laura and the team at cerus looked at the reduction of babesia either by concentration or by total log reduction. So you have a five to six full log reduction, which actually corresponds to about the highest titer of babesia, at least, that we've seen in blood donors, which is three times ten to the sixth.

So in conclusion or summary, tick borne diseases are an increasingly recognized threat from a wide variety of agents that included viruses, rickettsia, spirochetes and protozoa. Why are they increasing? Is there increases in recognition? Are there increases in tick density? Expansion of the range of our reservoir mammals or encroachment of humans into wooded areas?

So it's probably a combination of all

of these. Interventions are not widely available, may have long development times and are costly. So we know a donor history is not effective whether we ask donors about a history of babesiosis or a history of tick bites, leukoreduction as I mentioned is marginally to not effective, including anaplasma, borrelia miyamotoi and actually ehrlichia ewingii.

So testing, probably the best thing to test for if we do need to test is NAP, because these are most timely related to infectivity, pathogen inactivation is effective, currently it's not available for all components and in order to displace testing it would need to be mandated so that all components were treated.

So -- and this will come up later today, processes for determining when decisions to do more, what should we do with these agents are critically needed.

So thank you for your attention and I can answer questions.

DR. LEIBY:: It must have been crystal clear in that case.

In any case, we are at a point for

another break. As you can see breaks come more often because your attention spans are getting shorter and you need more caffeine.

We'll be back at 2:40 for the final session. And so please hurry back. Thank you.

(Recess)

DR. LEIBY:: Okay. Welcome back. We are now into the home stretch. No more breaks, you must carry on through the remainder.

It's my pleasure, at this point, to introduce Dr. Louis Katz. Let's see, Dr. Katz completed his residency in internal medicine fellowship in infectious disease at the University of Iowa Hospitals and clinics in Iowa City. He's been in Iowa for a long time with Mississippi Valley Blood Center. His most recent position is with -- he's the chief medical officer at America's Blood Centers, which he will be retiring from in August.

DR. KATZ: Refocusing.

DR. LEIBY:: Refocusing and returning back to Mississippi Valley Blood Center. He resides in Iowa. And Lou is going to talk about mitigation -- or mitigating infectious risks of

blood transfusion. Lou.

DR. KATZ: Okay. How does this work?

DR. LEIBY:: He'll bring it up. You just need to click and --

DR. KATZ: That one. Okay. Got it. Okay. So I am getting paid by Terumo, but that

shouldn't influence this talk -- a little by Terumo. So this is my six legged stool, you only see five,

but it will turn into six legged stool, upon which we build transfusion safety.

The first three approaches are -- can be quite pathogen specific and they may include education, illustration of risks and behaviors in testing for specific pathogens. The last three, including -- if I can make this work. Whoops, how do I go back? Oh, I can't see a thing. Oh, I thought I did that. Okay. There is it. I've added in pathogen reduction. That's new, not available for everything, only platelets and plasma at this point. In fact, in the U.S. and worldwide and I would be remiss not to emphasize the importance of the decision to transfuse, so to the degree that you don't give a product, the

risk of transfusion transmission is zero and I think the importance of judicious transfusion is sometimes under emphasized at meetings like this.

So this is donor qualification at the beginning of that six legged stool and this involves donor education up front, donor questioning and physical examination of a donation and the question is, does it work? And it depends on what bug you're talking about. This is the paradigmatic demonstration of the impacted donor qualification.

So here you see the entry of HIV into the United States. The first Aids cases reported, transfusion associated Aids at this point. And then we start with high risk donor education, donor screening questions about specific behaviors and only here in '85 do we introduce donor screening by which time the risk in San Francisco had fallen by an order of magnitude, approximately, 90 percent. So the answer is, yes, with a specific agent, with a well recognized set of associated behaviors, donor qualification short of testing is quite remarkably effective.

These are the three biggies. This is ARC data, first time donors versus sort of the population alas CDC, this is -- I think, Roger was the one that published the data in this table.

So you can see the U.S. population rate according to CDC and the American Red Cross first time donor rates, this is about 15, 20 years ago and a rate ratio. So that donor qualification, all the things that we do to qualify a donor, educate them before they come in, examine them and screen them with history questions. Once they get to the blood center -- result in or around an 80 percent reduction in first time donors of the risk of the three classic transfusion transmitted viruses.

This is Malaria, another example where I think donor qualification works pretty well. Back to 1963 and up to 2013 and you can see associated with the Vietnam War and an influx of people from south east Asia, as well after the Vietnam War the prevalence of Malaria -- cases of Malaria in the population increased at that time and these are the transfusion transmitted cases in the bar. And you see we've fallen down now to

about one case a year. And although I used the surveillance summaries from the CDC to make this graph, I am subsequently aware of about one case a year since the 2013 report.

So that's 12 million donors a year with a very, very high and increasing prevalence of international travel amongst our donors and I think you can see that we do a pretty good job of controlling Malaria. Of course the behavior is pretty dramatic behavior, have you been to subsahara in Africa, primarily? That's a pretty straight forward question to ask a donor, it's not very complicated at all. And it appears to work very well.

This is a little shift in emphasis. This is work that we did at my old center before I moved to ADC where -- with a company in Virginia, we developed an audio visual touch screen computer assisted screening interview and implemented in 2001. And we compared historical face to face first time donors with first time donors subsequently screened and demonstrated approximately 90 percent increase in the elicitation of high risk behaviors that led to HIV

deferral.

So it isn't just that you do donor qualification, it's how you do donor qualification that may be important. And I'll try to make the case it may also depend on the specific pathogen.

This is Malaria in the same system, it didn't do anything for Malaria. Why would that be? Asking somebody if they've been out of the country in the last three years is different than asking them if they've had anal sex with another male recently, right?

So there's an entire sort of cognitive science in -- gets into things like social desirability or distortion, that sort of thing. So it isn't what you ask and/or how you ask, it's both. And so it worked actually quite well in our hands for HIV risk behaviors, but it had really no influence at all on post donation information, subsequent report of deferrable behavior by our donors.

This is *B. microti* and *Anaplasma* and this is David Leiby's data, which I really love and what you see here is people who -- donors who

reported a tick bite or had no tick bite, both for the two bugs and then serologically tested and it was a coin flip.

The history of a tick bite or no really didn't predict whether people had serologic evidence of infection with these bugs. So what works for HIV or Hepatitis may not work in this case, specifically, for tick borne infections.

You might speculate that many of those at risk for tick exposure might be looking for and removing the critters before they transmit and so that here are biases in asking the question that may confound its impact on predicted value.

Now how many antidotes does it take to make data? This is a series of telephone interviews that I did at my center. With 100 consecutive donors who answered yes to the donor history questionnaire, do you have a history of babesiosis or chagas? This was before chagas screening in 2007 and I called them up and did a short telephone interview. I found 72 of 100 donors and the motile response is shown at the bottom and that's unprintable. When I called these donors they said, I have no idea what you're

talking about, you d...d...d...d.

So does donor qualification work?

Yes. But it depends on what you're asking, how you're asking, face to face, paper interview, computer assisted interview and it may differ across who you ask, first time donors, experienced donors, that sort of thing.

It works. I have a very strong sense with the tick borne infections that we're asking about today, that it's not going to be effective.

Leukoreduction you've heard about, the precedent was these two most specifically CMD and you've heard the impressions of both David and Susan about the tick borne agents that we're talking about. Certainly not -- and maybe partially effective based on some of the data you've seen, but it's not -- if we decided that mitigation is necessary, I think leukoreduction, one or our process steps, is not going to be effective.

We then move on to process control and quarantine. This is a GMP requirement that we adapted at the urging of the Food and Drug Administration in the mid-1990s. These were

long associated with the pharmaceutical enterprise and we started in the wake of HIV and non A, non B hepatitis and really have fully integrated CGMP into our chromosomes at collection facilities over the last 20 years.

The require a broad range of processes and procedures to address issues like training, quality systems, qualifications and monitoring of automated systems, a very wide variety of -- a big chunk of CFR that we have to pay attention to. And in this table what I've shown you is in my distillation of blood product deviation reports to the FDA and this was when? 2015, fiscal year 2015. And this is 18,000 BPDRs and let's say between 12 and 14 million products collected during that time. And 2,100 with any ID risk that should have resulted in deferral.

That doesn't mean the donors were infected, it means they had a risk that should have resulted in their deferral and didn't, .16 percent. And when you look, specifically, at viral testing which is the core or protecting against the pathogens that we're most interested in at this point, even much lower.

So GMP results or contributes to really a substantial level of safety in the blood supply and I'm not sure that we have specific GMP interventions to add onto what we do now that would have any relevance to ticks, specifically.

So then we get to invitro blood donor testing and you've sort of seen this, this is the list of the things that we're doing and when we started doing them. Syphilis in the 1940s was the first one with the Wasserman test. One of my old mentors who some of the older people in the room might remember, Elmer Degowan, after whom the Degowan Center at the University of Iowa is named, also advocated in addition to the Wasserman test, physical examination of male donors genitals and it was not widely adopted. Never the less, we haven't seen transfusion trans -- recognized transfusion transmitted syphilis since the late 1960s.

And then you can see the rest of them that we added on over a long period of time. ALT went away and HIV P24 antigen went away. Everything else has been as persistent as a tick.

B microti antibody and/or PCR actually,

I think nucleic acid testing and/or antibody will be coming some time to a theater near you.

These are estimated window risks from the big three, let me call them. And as you can see one in a million or less, the HBV data are a little bit confounded by what we believe might be the infectious dose for hepatitis b. the rarity recognized and reported transmissions are much less common than the estimates here and I think that's a combination of a couple of things.

One, the models that we use really are worse case models and I think that's appropriate when you're modeling transfusion safety within reason. A substantial fraction of transfusion recipients die of their underlying diseases before some of these infections would be discovered, depending on whose data you read. If you're sick enough to get transfused, you have a 50 percent probability of dying within the next two to five years. It depends on the data set that you look at, but a lot of people don't pass the incubation period for adverse outcomes, at least these three.

And there may be a bias against

reporting because of legal considerations as well. So these are the estimates, primarily via the incidence window period model, but they are far higher estimates than what we actually observe.

So here's tick borne -- I'm just going to go through this stuff very quickly, because I think actually Susan covered it quite well. We can test for tick borne agents, this is the immunetics enzyme immunoassay and if the cutoff is here you can see that you get reasonable -- in 18,000 donors, you get reasonable discrimination in a non-endemic and endemic areas between infected and non-infected as compared to clinical babesiosis cases.

So you can build a task with performance characteristics that might be acceptable. Immugen has built a PCR test in an indirectless antibody that Susan referred to and I'm just showing you the results of two studies just to show you that testing can interdict the tick borne infection and the important stuff is here. This is the Rhode Island Blood Center, they began selective donor screening at the request of their

clinicians in 2010 to reduce incident of babesiosis in these groups, okay.

Subsequently they've screened almost 35,000 of their 600,000 donations and they've had no transfusions transmitted babesiosis from screened donations versus 24 from unscreened. These are my statistics, because when Carolann gave me these data she hadn't done her chi score, but that's highly statistically significant. And so it is certainly proof of concept not surprising to any of us that you can interdict affected units with a screening approach.

Same thing from the ARC, essentially no transfusion transmitted babesiosis from screened and 14 from unscreened in their north east region. I think I've showed that data correctly, Sue, if not you can stand up and rag me.

And then we get to the holy grail. Those of us on the transfusion transmitted diseases committee who are beyond a certain age that CDC would call old and that, of course, pathogen reduction or pathogen activation.

I always like to -- because I'm old now and I need lists to get through the day, the good

stuff here and the bad stuff here. Broad spectrum proactive, that's the main thing that really attracts me to pathogen -- it's proactive. So you'll be able to kill many known, some unknown and emerging bugs without worrying about whether you've built a test or started asking donors about the intimate details of their sex lives will probably prevent grant versus host disease and that means we don't have to eradicate, which means we can get rid of our cesium, which means that we can keep the nuclear regulatory commission out of our blood centers, that's a good thing and it is conceivable that we could reduce testing requirements, although I fully intend to be cold and six feet under before that happens.

There is theoretical toxicity. By the time you get through the pre-clinical and clinical requirements for licensure in the U.S. I think that we will all agree at the end of those processes we're going to wind up with theoretical toxicity risks, but a huge data set suggesting that the approaches are safe. While we will never, ever get a neonatologist to agree with that statement, I think those of us who take care of

older patients will probably agree.

There are lots of effects on products and this is really a hurdle that we're seeing, in particular, with the application of these processes to platelets, where the guard bands required in the process result in substantial loss of product, the inability to treat many collections and possibly storage lesions of unknown clinical significance. So this is really important to think about, whether the clinical impact is relevant or not we don't know. The experience with both of the platforms, the one that's available in the U.S. and the other that's in clinical trials in the U.S., clinical experience rest of world suggests that pathogen reduced platelets treated with riboflavin uv or with S-59 and illumination work and will prevent bleeding when used in appropriate patients.

Cost, big issue, nobody wants to pay more for anything anymore and perhaps we're talking about a platelet costing -- it depends on who you talk to 50 to \$100 more, depending on many things, when it's pathogen reduced. And then there's risk benefit and cost defacacy. I think

I can make the case for platelets because of bacteria. I'm not sure I can make the case for red blood and whole -- red blood cells and whole blood in the U.S. because the infections that we're concerned about are so rare, that adding 50 or \$100 to the cost of a red cell may not pass muster of the health economist. That doesn't mean that the products won't get approved, but it may certainly be deterrent to deployment in the real world.

These are the approaches and U.S. status -- this is an old slide and if I missed anything, I apologize. So cerus is making intercept, which in platelets and plasma is S-59 a psoralin and uv? S-303 for red cells is frangible anchorlinktor effector with glutafont thione radiation and approved in under development clinical trials starting. Terumo BCT dosmeriasol, which is riboflavin in uv light and clinical trials for platelets and whole blood are -- the platelets are under way and enrolling patients and whole blood will start imminently I'm told as chair of the DSMB.

Macopharma had plans but no longer has

plans for metholene blue. Octapharma has an approved product in the U.S. solvent detergent pool plasma, not widely used and I think not widely used primarily because of expense.

So these are vector borne bugs and the impact and Sue showed you some of this data and I'm not even positive they're completely up to date. I wasn't aware of Laura's data that you showed, which looks a little better.

This, of course, begs the question of the titer in a component and the minimum infectious dose. So these all, in general, exceed our ability to spike into the component -- the bugs. It doesn't answer the questions of titers in clinical illness or in subclinical illness in a otherwise well blood donor, so caveat emptor, as I say here.

I stole this slide from Ray Goodrich, who I think is going to speak next and, basically, the point that I'm trying to make is if this is the log pathogen titer and this black line represents the capacity of pathogen reduction, the real question is whether and for how long the pathogen titer exceeds the capacity of the

pathogen reduction process?

So if you're talking about parvo virus B-19 or hepatitis b, that may be considerable. If you're talking about the tick borne agents we're talking about today, I have a very strong sense it's not an issue, but show me the data.

And then there's the decision to transfuse and as I said, if you don't transfuse a unit, you're not going to transmit a bug. These are data from 2008, 2009 from Dana Devine, when U.S. red blood cell transfusion was around 50 units per 1,000 population, that's over here. At the same time our colleagues in Canada were down around 30.

Current estimates in the U.S. put us right around here. So we've knocked about 40 percent of our transfusion off the top. This is red cells. Actually plasma and platelets are flat to up minimally. Appropriate utilization based on high quality data and adherence to clinical guidelines I think is a critical element in this discussion, so I'll get off my soap box.

And you've seen these things, these kinds of maps. This is ixodes, this is a really

neat article that I think is as good as anything else, that shows using all kinds of things, climate and humidity and a variety of other inducives to project where ixodes scapularis is going to be out to 2080 and as you can see it's getting bigger. And I don't know if this data is accurate or if somebody else's map is better. The point that I want to make is, however we look at our assessment now about the need or no need to mitigate any of the tick borne agents we've discussed today, this is a set up for Judy Leach Bennett, this is a natorative process and I expect that 20 years from now or 10 years from now, we may be having different discussions based on things like the extent of the vector, environmental conditions that support infection of ticks or transmission from ticks, demographic and behavioral things that bring us into contact with ticks.

So, I think that's all and I'll quit.

DR. LEIBY:: No questions? Clearly beginning to run out of steam with no questions. Well, hopefully, Ray can take care of that. Our

next speaker is Dr. Ray Goodrich. Ray is now the executive director of Infectious Disease Research Center at Colorado State University, where he has responsibility for oversight of the biopharmaceutical manufacturing and academic resource center, the regional biocontainment labs and the research innovation center.

Many of you have known Ray in a past life, I think. He spent many years of medical research for, as you said, for over 29 years, has over 50 patents. We probably best know him because he was involved in Terumo, which is earlier choridium and I don't know all the other different names of these companies, which they now seem to change almost yearly.

Most importantly he also is an adjunct professor in chemistry at the Ohio State University. So I will introduce Ray.

DR. GOODRICH: Yes, David recognizes by law we have to say the Ohio State University. I've caught myself a couple of time saying the Colorado State University.

Thank you, David, for the invitation to

come here and it really is my pleasure to come and talk about this topic. And David had asked me to speak about the conceptual framework for test development, I actually changed the title a little bit, because what I'm going to do is talk about the conceptual framework for development period in a very general sense.

As he mentioned I do have an administrative appointment at Colorado State University as the executive director of the Infectious Disease Research Center. I also have a faculty appointment as a professor of microbiology, immunology and pathology.

In terms of conflict -- let's see if I can -- there we go. I do have a consulting relationship to Terumo BCT. As David mentioned, I was a long term employee at BCT, I was there for 20 years. One of the conditions they asked upon my departure was to allow myself to be available for consulting from time to time. Much to my amazement, every now and then they do listen to something that I have to say.

I think Lou did an excellent job of sort of outlining some of the issues associated with

an approach that could be used to address the issues that we have here today. But the basic theme that you're going to hear me talk about today is that it's not about the technology, it's about -- the technologies exist whether they're testing or they're pathogen reduction or inactivation technologies, they exist for us to be able to apply in these settings.

So the issues about whether we do or we do not have much more to do with decision making, risk benefit analysis and with approaches that we take in implementing new technologies in society or developing new technologies from the standpoint of an industrial group. Those are the things that I'm going to focus on.

So with regard to PRT, there are pluses and minuses that are associated with them, there are expectations for it, there are realities that are associated with it and there's a balance that has to be played off in that regard. So why do we bother with even considering this? Well, I paraphrased Henry David Thoreau here and said that we deal with this and we consider it because it is a technology that can strike at the roots

of the problem.

If we can apply something, as Lou said, in a proactive fashion, we have a way of potentially heading off issues that may occur before they become problems that we must deal with. That's really the potential benefit associated with using a technology platform such as PRT.

What about testing? Well, equally, there are number of expectations, I think, that we have around diagnostics and there are also a number of realities that are associated with them. And we have seen this implemented with success over the years. It continues to be implemented with success in many approaches in dealing with agents as they emerge into the blood supply in particular.

So, again, why bother? And, again, it is because it is a fundamental technology that can strike at the roots of a problem, the issue of contamination of certain agents in the blood supply.

Now one thing that I will say and you'll see this in the context of some of the discussion

that follows is that an advantage that diagnostic tests have over PRT as a diagnostic tests are done with a small portion of the blood that is transfused and PRT is a technology that is done to the blood that is transfused. And from a decision making and a risk benefit standpoint that is always going to be a situation which demands more question, more analysis and hence, more development costs associated with it. And I think that may address some of the issues in terms of why the timeframes for adoption or implementation of some of these technologies differ so much.

Again, my focus is really going to be more on the fundamental issue, the barriers that industry faces from a social, economic and regulatory perspective in developing new technologies for blood safety in general.

There was a story about Howard Schultz the founder of Starbucks telling a story about when he was explaining to investors that he was going to open up a store that was going to sell coffee at about \$4 a cup. And he would get the response from the people in the audience that that

makes no sense whatsoever, coffee? Only coffee? I could go down to the local diner down the street and get a cup of coffee for \$.10, I get free refills and if I'm hungry I could buy a piece of pie. How does that make sense? And his response to that was, it's not about the coffee, it's about the environment, it's about the bringing people together, a place where they could go and read and talk and have a nice place to have a cup of coffee.

It's not necessarily about the technology, it's about all the factors that surround it in terms of whether or not these types of approaches are adopted.

So, what are some of the challenges for implementing diagnostics and pathogen reduction from a commercial standpoint? It's the fundamental problem of the return on investment or ROI. Investment is directly proportional to the perceived return. The perceived return is directly proportional to product pricing. The perceived return is directly proportional to the market size.

A fundamental issue that has faced -- when I put this slide together, actually,

several years ago I said it's relatively fixed and constant for blood banking and transfusion medicine, but in more recent years, what we've actually seen is a decline in consolidation. That pressure goes across the board not only to the groups that are collecting and processing blood, but also to the groups that are developing technologies to be implemented related to blood safety, blood collection and blood processing.

The cost of developing new tests of PRT methods are very large. New diagnostic tests on average run about \$30 million. I might be off on that figure. There's a range anywhere from 20 to \$100 million from concept to full implementation.

New PRT methods, and this one I'm fairly confident in, having firsthand experience, there's an average of about \$500 million per method ranging from 100 million to greater than a billion from concept to full implementation.

Now just as the blood banking community, insurance industry and government health care reimbursement groups have to do a cost analysis when they implement policy or new programs so too must the industries who develop

these processes.

That poses the challenge, as I mentioned, that when investment is high and the expected return is high, the cost of the product will naturally be high. If the hurdles to entry are high then -- and it requires large investment in order to jump those hurdles, the expected return and hence the cost of the product is going to be increased.

Now this principle as fundamental odds with the blood banking industry. What do I mean by that? This is a paper and I thought it was really well done because it started to address this kind of issue. When it was done it was a study done back in 2004 about the implementation of leukoreduction and it's in Dutch and in French and also in English and the main tenant of this piece was this last paragraph here, why were there issues with the implementation of leukoreduction technology? The authors of this report indicate that one of the biggest factors was that to maintain the trust of the disinterested volunteers blood has to be safe at an acceptable cost. If costs increase over a certain

threshold, volunteers may perceive this as exploitation.

I tried to put this in the context of my own personal experience. My wife and I donate some of our used goods to Goodwill from time to time. If you ever go into a Goodwill Store, I will tell you there is no one playing the piano in the atrium or offering you Perrier while your spouse or significant other tries on clothing. There's a place that says men's clothes and women's clothes in a pile.

The expectation that I have as a donor is that I'm doing this because I want those materials to go to people who can benefit from having them at a low price. If I walked into the store and I saw those things and I saw my used clothes or my used toaster being sold at retail prices, I'd probably think twice about giving my goods to Goodwill. And I think that that mentality applies in terms of our blood donor populations. Blood is free because it's freely given, that's at least the perception that holds around this.

So our challenge is basically to

continue to find ways to fund and support research and development activities given that there are these constraints of economics on the medical industry and the desire of the investment community to provide rapid financial returns.

What options do we have? Well, we could wait for epidemics. When an epidemic comes along it's obvious we need to do something, right? We can lobby public opinion, we can parade people in and talk about the disaster that occurred in their lives and how it would have been good to have something to prevent this.

We can address the concerns over safety and efficacy by large scale trials, investment and development and surveillance efforts to stay ready and capable of responding. The problems are expense, time and you can never prove a negative, I don't care what your sample size may be.

I added one more to this and that's the modern mantra of get the FDA to approve it. Because if the FDA says we have to do it then all of these other questions go off the board. We don't worry about money, we don't worry about

logistics, we just have to do it. It's a possible approach.

So another question that we could have related to this is understanding this -- and this is a question that was posed to me and several others a few years ago as part of the advisory committee on blood and tissue safety and availability, is how do we do new technology introduction and optimal blood service care in a period of time where we need to do this that's economically sustainable using risk based decision making while still allowing for continued innovation?

Well, one factor we have to take into account are the regulatory requirements. Let me be clear on this, the role is needed. What we have to do is understand the factors that impact the decision making and by understanding the dynamic to optimize the process.

I'll give you some examples. Everyone wants safer, better blood. I have not met anyone in my years, 29 years plus being involved in blood banking and transfusion medicine who said they don't want this. Okay. But no one wants to take

a risk on new approaches to achieve this in the absence of either a crisis or a major push by the healthcare community or the public at large.

I firmly believe that perception can become reality only if the cost of developing and implementing these approaches are low.

Regulatory hurdles and commercial realities. Well, again, regulatory authorities insist upon a large amount of clinical evidence that the ultimate products are safe and effective. I, for one, am glad that they do. I remember a conversation, the first meeting that we had for the medical device innovation consortium and Dr. Sheran made this made this statement and I wrote it down and I kept it with me. Said it's not a question of needing data and evidence, it's a question of how best to attain it to satisfy the reasonable and mandated needs of the public. And I think that is our challenge, that's the approach that we need to take.

There's also the consideration that we have to give when we do this of the difference that exists within the communities minds about the nature of transfusion products. I tell this

story about the fact that I was in speaking with someone, a surgeon, many years ago, talking about a product that corrects INR, has been studied very widely in a number of different indications, safety profile is fairly well known, aptly demonstrated and his question to me is, is that a new factor concentrate that I haven't heard about? I said, no, it's called plasma. There was an inherent belief within that community of people that we spoke to that a manufactured product was inherently better than the natural product that was derived, even though one product was much more expensive. So in that case it wasn't a matter of money, it was a matter of the perception of the value around that particular product that was being used in that setting.

So several years ago I gave a presentation at the ISBT talking about this issue and I said at that time that I believed that enthusiastic adoption of new blood technologies would await clinically demonstrated advantage, that we have to make a case for why we should do these things. A few years later a very similar message from this pulse of the industry was a

medical technology report that came out in 2011 talking about the ability to demonstrate how these new technologies are improving health outcomes has to become an integral part of the decision making process in adopting or not adopting a particular technology.

If that is, indeed, the case, we also have to consider something else and that is the human factors. Now when I talk about human factors I mean the way we make decisions.

Institutions are made up of people, people set policy and practice, hence we need to understand what makes people tick, no pun intended there.

So how do they think? How do we think? One way of looking at this in terms of a decision making context -- I love this book, it's called, Thinking Fast and Slow by Daniel Kahneman and I would follow the advice of what's on this label here and look inside, it really is a good text.

And one of the points to be made here is that we have to realize how we think to understand how we make risk based decisions. And as he points out here, that's not a criticism of our decision making, it's just an understanding

of the reality of how those decisions are made.

One way of looking at this in a simple straightforward way is to say, Kahneman and Tversky are the individuals who developed this, they won a Nobel prize for it, in fact is model for risky choice, the preferences that are related to risk are reference dependent. In other words, you make the decision based on the circumstances that you're in.

So I put this in the context of saying, why is cure easier to sell than prevention? Well, cure, in this case a cardiac bypass procedure that someone is undergoing to deal with heart disease, you are facing an immediate risk and threat. Prevention, taking a baby aspirin everyday to prevent the build-up of plaque sometimes is much harder because you're not facing the -- it's easier, just take a baby aspirin, there's no procedure involved. But it's harder because you're not facing the immediate risk decision and the consequence of the failure of your actions to do so.

So there are some key questions to answer when we look at this in terms of bringing

new products, whether they're new tests for something like a tick borne disease or pathogen reduction technology when we brings these to bear. We have to ask ourselves, do we operate under scenario one, nothing to lose versus potential gain or scenario two, certain loss versus potential gain?

The answer to those questions are going to determine my opinion, the prospects for new products at any given geography or point in time. I use some specific examples. I love giving this talk here in Washington D.C. because I always tell people, you know, in answering the question, why can't we go back to the moon? If you go to the Air and Space Museum and you look at the things that we sent people into space in the '60s and '70s they look like they were actually made out of old car parts from a junkyard. And you look at what we have today just in the jets that we fly and that's Star Trek, that's modern, that's fancy. It has nothing to do with the technology. At the time we went because we took the risk of maybe a 3 percent chance that the people that we sent wouldn't come back and we did that because we were

chasing the Russians, because national pride was at stake because our political position in the world was at stake. And today we wouldn't do that unless there was a 99.999999997 percent chance that they would come back. The dynamic is just very different and the decision making is very different.

My 10 year old asked me recently if we would ever go back to the moon? And I said we probably would when we run out of resources here that we have resources on the moon to replace.

I use this example from Hurricane Katrina. People have heard the story that for many years it was known that these barriers down in New Orleans would withstand a Category

hurricane, so why didn't someone do something about it? My question is, was it a mistake not to prepare for a Category 5 hurricane, the cost was several billion dollars. Every dollar that wasn't spent there was spent on things like roads or hospitals or education in the State. Really, you might look at this and you might say the only group that made a mistake was the one administration that was in power when the

hurricane finally hit. Okay. So multiple factors contribute to this.

It was interesting because several years after this event, my wife and I toured some of the communities that were impacted by this with families that were from those areas and was interesting to hear the perspective. At first we were told no expense would be spared, about a year went by and people were saying, well you know we need to look at this a little more carefully to fully understand what the expense is going to be. Another year went by and people were saying, well, you know, could the local government provide the support to do this? The federal government can't pay for it all. By the third year it was almost as if people were saying, so what's a little bit of water? People just got wet.

And those levies that were rebuilt were never rebuilt to that higher level of standard, because it's a once in 100 year event.

So how do we foster continued innovation? One of the questions coming forward now? Sue Stamer accused me in the hallway of being an optimist. I told her I am a very

optimistic pessimist. When I thought about it that was actually a much kinder statement than what Daniel Kahneman says here. He actually says that to be a scientist you have to be delusional, because you have to have a mindset that allows you to persist in the face of many setbacks.

Absolutely true.

People who are in companies face an incredible dilemma being innovators. They're told they need to be efficient and they need to be creative and if you look at the requirements associated with both of these, I think the thing you will notice is they are totally contradictory. So the question is how you're able to do both and often times you end up doing neither.

You also have to deal with the issues of going against human nature in our decision making processes, sometimes it is counter intuitive. There's a story about a jet plane that left Brazil flying to France a few years ago and the plane crashed, unfortunately. They did recover the black box recorder and they found that while the pilot was pushing down on the wheel, the

copilot was pulling up. Now who was right? Actually, it was the pilot because when you stall, which is why they were losing altitude, you don't try to climb, you actually try to dive so you put air through the turbines and restart the engines.

Think about all the hours that those pilots probably spent in training, yet when it came to that moment of decision making, the copilot, at least, was doing the opposite of what his training said to do, just based on human nature.

So the issue here is in an era of declines in revenue and in market size, what should you be doing? It's hard to convince people to say invest in new diagnostics or new methodologies for blood safety, it's counter intuitive to do that, although that may be the right answer. I believe it is.

Organizations also are faced with the fact that innovation comes incrementally for a reason. I saw this slide a few years ago, an advertisement was sort of like one of these draw me and you might have the talent to be an artist, send in your \$25 and we'll give you a kit that you

can learn from.

Well, to me, innovation requires leadership. Leadership, to me, is defined as movement in the face of risk. And it also requires persistence. There is no idea I have ever met that is so great that it can't be overcome by even a mediocre bureaucracy. Okay.

So, again, I'm going to go to recommendations here, because I want to leave you with something I hope is positive. I think there are ways that we could deal with the issues that we face in terms of adopting these new approaches. One is, I believe, to create forums for discussions and collaboration between industry private sector and government agencies.

To me the example is medical device innovation consortium. I really think that's an excellent program. I'd like to see it more broadly. A place where people could come together, have discussions about how national policy or national programs might be established that benefit the community. Develop tools for risk assessment that includes public opinion and perceptions of issues. I think the next talk is

going to deal with one of those.

If we have meetings like this we have to talk to more than people other than ourselves. We have to talk to the communities at large, the public, to raise their awareness about the importance of blood. I had a conversation at lunch about the fact that blood is an essential. Think about medical procedures, surgeries, treatment for cancer without a safe and adequate blood supply, yet it's a commodity product in most people's minds. We have to change that perception if we want to continue and invest and see improvements in the things that we do from the technology standpoint in this field.

We have to foster innovation through research funding. I really believe that a large part of the advancement will come through things like SBIR programs and why do I believe that? Because in large corporations it's very hard to get new ideas going and started and the reason for that is that there's a problem with disruptive technologies and the problem is, they're disruptive. They disrupt financial plans, they disrupt financial revenues. They cost money to

invest in and so there's a tendency not to want to disrupt things but to maintain the status quo.

IBM in the 1970s had all the talent, all the money, all the knowhow, so why didn't they invent the personal computer? It wasn't until they took some of their best and brightest people and sent them from Schenectady, New York to the middle of Kansas and told them, go do this, that it was able to get done.

And, finally, I think we have to create a culture that does not punish small failures so as to prevent big ones. Failure is always an option. Anytime you make a decision your decision could be wrong.

So the statement, failure is not an option, does not exist. Sometimes the failure is not making a decision. So we have to find ways to be able to allow people to make decisions even in the context that sometimes those decisions might be wrong.

So, I think I'm going to put in a plug for a conference that we're having at Colorado State University. It's much broader than just transfusion transmission, but it does include

that. It also deals with innovation and infectious disease research challenges and opportunities. It will be June 7th to the 9th. There is a website that you could go to, IDRtalks.colostate.edu in order to find out a little bit of details about the agenda and if you're interested in this field and this area these are some of the things that we'll be talking about, ways that we could bring new innovative technologies to bear on problems that are of public interest.

So thank you very much for your time and attention.

DR. LEIBY:: Any questions for Ray? Very thoughtful. Our last speaker today before the panel discussion is Judie Leach Bennett, and Judie is the director of Canadian Blood Services' Centre for Innovation, which facilitates research and development, education and support of safe and effective system of blood and related biologics for Canada. Previously, Judie held legal roles from the Canadian Blood Services and with a Toronto law firm, where she conducted litigation focused on product liability and

health laws, including HIV, HCV litigation at all levels of court. She received a law degree from the University of Western Ontario and a Master of Laws from the University of Ottawa. She's here today in large part because she's active in supporting the Alliance of Blood Operators, and Judie actually chaired its initiative to create a Risk-Based Decision-Making Framework for Blood Safety, and that's going to be the topic of Judie's presentation today. Judie?

DR. BENNETT: Thanks very much, David. I just wanted to start out with one small disclosure. According to the CDC definition, yesterday, I became elderly, and I chose to celebrate by coming here to be with you, so I plan to enjoy myself during this talk, so let's get started.

As David mentioned, I was involved in creating the Risk-Based Decision-Making Framework for Blood Safety. That was an initiative of the Alliance of Blood Operators, and I'll just show you the schematic that is associated with the framework. What I should say is that, if you have a look, if you haven't

already, you can go on the website and there are resources and guidance really around each of the steps that you see here in the decision-making process, so around preparation, problem formulation, the participation strategy, assessments, evaluation, and decision, not a novel set of steps, but steps that we have taken the time, together in collaboration with members of a working group that really had people from many jurisdictions, and trying to tailor a risk framework specific to blood operators and to our blood sector context.

There's an underpinning of specific principles that guide the analysis in the framework, and those include risk- management principles and not unexpected, but again, very tailored to blood context, thinking about practicality and proportionality, thinking about continuous improvement, vigilance, along the lines of the surveillance we certainly talked a lot about today, and the notion of transparency and consultation.

There's also a specific set of guidelines around risk communication and

stakeholder participation. As we've heard today, and certainly Dr. Goodrich referred to it earlier, these decisions that we make don't happen in a vacuum. Blood is a ubiquitous treatment, it influences, and many people have a stake in the decisions that we make, and arguably, we have a duty around communication and characterization of risk, and also to engage those affected across a variety of stakeholders to engage them, to educate, and to have a dialogue and to gain input.

There's also the notion of assessment. Really, this process would be meaningless without really powerful, robust assessment in accordance with the discipline associated with the kind of assessment that we have, the quality of the assessment, the notion of not doing things in silos but doing them in an integrated way, knowing how to characterize uncertainty and making sure we account for that and apply evidence and also judgment.

Then, finally, the notion of risk tolerability, this idea that we all know instinctively how to manage very, very low risks.

There's an acceptance of the kind of risk, that low risks instinctively can be easily managed. We also have a sense of what constitutes a very high risk that is completely intolerable. But what we've talked about today is what happens in the middle of that continuum. What about those risks that we know we can manage, but then we have to decide the extent of the resources that we'll allocate to manage those risks, to what level do we manage those risks, and what is acceptable from a societal point of view. Again, we need to make the decisions, and we can't abdicate from those decisions, but we're doing that on behalf of our patients, on behalf of society, which is why we try to include this notion of risk tolerability, as challenging as it is, in our framework.

So what I'd like to do, first, I'll just give you a little bit of an update on where we are in terms of actually using the framework. We developed the framework a couple of years ago. We talked about it, we wrote about it, but now, we're starting to actually use it. We're starting to iron out the bugs in the process and really learn about and become more sophisticated

about what we're doing.

You can see some examples of case studies on the slide, where we've endeavored to use the framework. In Canada, we have applied it to our Babesia situation, even though it's a different situation than the one we've just discussed today in terms of the U.S. circumstance, but I'll come back to that and kind of demonstrate how we use the framework in that situation.

We also have a couple of case studies with respect to HTLV, both in Australia and in Ireland. In both those cases, taking slightly different approaches, they really came to the decision to discontinue universal testing and to test first-time donors only, and so that was an interesting application of the Risk-Based Decision-Making Framework.

We've also had some early work done on pathogen inactivation, but very early and not really well-developed as yet. There has been an exercise going on in the U.S. context around Babesia led by AABB. We'll probably see some results coming out of that soon. In Canada,

we've also done a CMV test case -- and I'll talk about that in the minute -- and some other work has been done and is underway around various donor deferrals.

So people are testing out the framework, trying to get results and seeing how it can inform decision-making. I would say the feedback is generally good; people find certain parts clunky at times. As they use it, however, they determine how to become efficient and streamlined with the tool, and in large measure, the feedback is that it is a nice, explicit, deliberate checklist or process by which one can include all of the kinds of factors we've talked about today, the very specific and quantitative, epidemiological information, the clinical information, but also, the social, the economic, the political, the ethical, as a way of incorporating all of those factors.

So what I'll do is just focus today on case studies that I'm most familiar with, the ones that we've actually done at Canadian Blood Services. What I'll do, I'll talk about both of them in tandem, because my real goal is not to talk

to you so much about the detail of those assessments, but rather to use them to illustrate the stages of the framework.

So the first stage in the framework is really this preparatory step. It was important to us to be explicit about setting out some initial tasks that one does before diving into those analyses that we're all so familiar with in terms of the IP data and our thinking around surveillance and that sort of thing, just stepping back and thinking about precisely the nature of the questions that we want to answer, who can best answer those in terms of expertise needed around the table, but also thinking back to those policy foundations that I talked about and making sure that we are applying those risk management principles, and we're thinking about the excellence and quality of our assessment, and we're thinking ahead about the tougher risk tolerability issues.

So in terms of launching the analysis, frequently, we're not going to reinvent the wheel, so we're looking at the pertinent literature, we're looking at expert advisory

committee recommendations, and really looking across a slate of expertise, depending on the problem at hand, whether that's medical microbiology, epidemiology, transfusion medicine, health economics, if necessary, stakeholder engagement and communications, and risk management; there could be others. As I talked about, important to look at those policy foundations and then to look ahead to that analytical decision framework.

What I should also say here is that we have been thinking, as we go through each new case, well, as we think about, let's say Zika, as an example, where we had to make our decisions relatively quickly, is there some sort of rapid response tool that we could create that helps us to move through those, in 24 hours if necessary, and then loop back and do more extensive analysis later, so just so you know that that is under development, and we're thinking about a tool or a checklist that can be used in those rapid response situations, always with the underpinning of that broader guidance that's provided across all those stages in the

framework.

Moving ahead to problem formulation, basically, the purpose of this stage is to really define and characterize the problem in order to identify, well, what is the question we're trying to answer, what's driving the decision, and then very early in the process, we actually try to develop the risk management options. The reason why we do that early in the process, even before the assessments are done, is because then they make the assessments very specific. We're constantly gathering data to evaluate the efficacy, the feasibility, the appropriateness of those various options. At times, some of those options drop away after those assessments are done, but that's the reason why we do it fairly early, and it's an emerging best practice in risk-based decision-making to spend quite a bit of time doing this framing exercise, because it really drives you to what you're trying to answer, as opposed to diving right into the data right away, and then coming up with an answer was really not precisely the one that we needed.

In terms of illustrating that problem

formulation stage, I'll just refer then to the CMV testing case study that we did in Canada. I don't need to tell this audience about how to characterize CMV as a risk, but just to say that this is an important piece, an upfront piece, of a risk analysis. We do poll what we know about, let's say in this case, the given pathogen. We want to know what its features are, whether it can be transfusion-transmitted, what's the likelihood of that, what's the window period, what kinds of patients are affected. All of these things come together in an analysis or a risk characterization that I think we're all very familiar with, this is what we do. Just for the purposes of the case study, like many jurisdictions, CBS employs two strategies to reduce risk in this case, so we have pre-storage leukoreduction for all donations, but we also have been offering CMV antibody-negative inventory, and that's available upon request.

Now, interestingly, so we have a whole kind of retrospective set of knowledge around CMV, and then when I move to the other case study, the Babesia case study, in some ways, as we've

already discussed today, this is more of a prospective case study for Canada. We certainly have done our own data-digging and seroprevalence study, and we know that the black leg ticks are well established in the southern parts of Canadian provinces. We know that there's a potential for a small or slow increase over time. I think, as Susan has already mentioned, we have had an endemic case, so there is some endemicity that's been proven, and certainly a transfusion transmission case, which was a donor travel case in the case of travel up to Cape Cod. So we have these things emerging, but it's more that we just want to be ready. We just want to learn from the U.S. experience, and we want to be intelligent about how we prepare as the risk increases.

I just wanted to add some Canadian maps to all the maps that we're stopping up there at the border, and those ticks are actually making their way up and clearly established in the areas you see, and we do too have good summer employment for summer students intern in the tick industry. This is informing. We're getting so closely with Public Health Agency of Canada around this tick

surveillance and the public health surveillance to inform what we're doing.

So really looking at decision drivers, this is where we decide, what's really driving this decision. It could be a variety of things. It could be an emerging pathogen; that's a very common decision driver. It could be through changing evidence or increasing evidence or some new technology. We realized that we are able to withdraw an intervention, and we can potentially use the framework to analyze whether it's a withdrawal of the intervention -- we saw that doesn't happen very often when we looked at Dr. Katz's slide -- but potentially we could use the framework in that regard, and that would be one decision driver.

Another decision driver might be a new technology like pathogen reduction technology, so that too would need to be assessed from a risk perspective. What are the risks and what risk reduction can we achieve, that that excites all of us, but are there new risks that are also introduced at the same time, and how does that play into cost effectiveness and that sort of

thing? So there are various decision drivers that we could look at in the specific cases that I'm taking you through today.

In terms of the CMV testing case, we really wanted to look at our current CMV risk mitigation being currently undertaken at CBS, and is it really based on the data we have today, is it proportional to the risk associated with TTCMV, and then if not, what alternative strategy could be implemented, taking into account safety, and also, operational impacts and really looking at this from a practical and proportional point of view.

As I said, looking at the knowledge we have to-date, the increasing literature on the point and kind of retrospective, and then looking more prospectively at the decision driver for Babesia in Canada, really wanting to understand the current and the likely future risks of Babesia, and understanding the options that would be available to us to address that risk. Then what is a reasonable risk mitigation strategy to adopt, both short-term but also long-term, and then what would trigger us to go from scenario 1,

the current scenario, to scenario 2? Those are the tasks that we set for ourselves, and they really do inform all of the rest of the stages in the framework.

The final part of the problem formulation, as I said, is to try to elicit, as best as we can when we're coming into the exercise, what would the risk management options be? Almost always, there's status quo. We can state that as an option, so in this case, it was basically to meet all orders for CMV-negative product using antibody testing, and maybe add some physician education along the way, with the goal of reducing the order volume that was being requested.

We could stop providing CMV-negative product entirely and rely on leukoreduction alone. Then option C was trying to think about providing some CMV-neg product, but for limited indications. You'll see we have option 1 and 2, and the reason why we have that is that, as we were going through the exercise, we thought about a very narrow set of indications and kind of balancing what we knew in the literature, but also

balancing what we thought perceptions would be in our physician community, but then our National Advisory Committee on Blood and Blood Products, that is a national body that provides advice to the provinces and territories who essentially are operating the blood system in Canada, issued draft recommendations that really narrowed further the indication to intrauterine transfusion, and so we put in that extra option.

The next option is really just the same option, except with NAT testing. Then, finally, because we always want to be aspirational, we almost always seem to put pathogen reduction technology as a last option, just because we want to have it there. So those were the options that emerged as we discussed CMV testing.

In terms of Babesia, as I said, there was no way to elicit a list of options without trying to look at the current scenario based on the current risk, and the future scenario based on the future risk. As you might expect, in the current scenario, the option is really to maintain the surveillance by monitoring public health surveillance, tick surveillance, human

cases in Canada and the U.S., but also look at undertaking another seroprevalence study in our donors on a given frequency so that we constantly are looking back into our donor population to see what's happening.

In scenario 2, these are not novel options, but really they're the ones that emerge in terms of either stop collecting the blood in the endemic area, or focus on testing in that endemic area and then testing high risk travelers as well, or maintain a small inventory of Babesia tested units for selected patients that are high risk, then the ever present universal testing option, and then, finally, pathogen reduction technology. That's really option generation.

Once we've done that, we can move to the next stage. Again, we're not diving into those assessments just yet, because we're just going to pause, knowing everything we know based on the characterization, what we want to solve, and what the options are. We really want to just pause and think, what is our participation strategy? When I say that, I'm talking about risk communication and our obligations around that. I'm talking

about stakeholder involvement, depending on a stakeholder's level of influence and interest, their stake in the issue.

What I should say is that by doing this, we're not abdicating our decisions to stakeholders. We're not wholly giving over that responsibility. What we are doing is seeking input, we're establishing a channel of communication, and we're gaining information that will inform the rest of the exercise and build that channel with those who are affected by the decision.

In the case of CMV testing, what we knew was communication was going to be very important. Physicians in Canada have gotten used to a certain product availability, and so while some, downtown teaching hospitals in Toronto, for example, really have already abandoned the notion of wanting a CMV-neg inventory and that they strongly encourage us to make this change, there are other hospitals in the country that this is part of their clinical practice, and so all of this needs to be communicated. We need to share the information and the data that we're basing

this decision on, and so that is an important piece of the participation strategy for this particular case study.

We also took this to our National Liaison Committee that really has a series of stakeholders present, and also recognizing, in addition to patient groups, it's really, as I said, physicians, including that National Advisory Committee I mentioned, but also the provinces and the territories who direct and fund the health system in Canada.

In the Babesia example, we were very interested to hear from stakeholders. We took the issue to that same group that I referred to, the National Liaison Committee, and that has patient groups represented, clinicians, members of different provincial blood coordinating offices, everyone with a kind of stake in these decisions, and I thought the feedback we got was highly sophisticated and helpful. There wasn't a reversion to say, well, absolutely, you can only do universal testing and we don't want to hear about anything else. It wasn't that at all. There was a recognition that vector-borne threats

are becoming more common. They felt that, by doing this analysis now, it was a good test run for future disease threats. They felt that there did need to be this proportionality between the response and the threat posed. They really appreciated the regular communication and felt that that would increase knowledge and reduce fear around threats.

They also acknowledged and saw that this kind of surveillance, these donor seroprevalence studies, they come at a cost, and that this is a worthwhile allocation of resources and a proactive response. They also talked about different ideas about donor consents that would be ready at all times to do this kind of research. We haven't gone to our Research Ethics Board with that kind of blanket donor consent at this point, and we might just put that off, but we appreciated the idea that they saw that we needed to be able to act quickly and get information as needed.

Now, I'll move to the assessment stage. As I mentioned, this is a stage where we really dig deep and we do our best to pull all the necessary data so that we can look at the options,

evaluate the options, and we're looking at a series of quantitative and qualitative assessments that will inform the ultimate decision.

In terms of assessment findings, this slide does not do justice to the amount of work that was done on either of the case studies I'm showing you. In each case, blood safety risk assessment was completed, a budget impact assessment, operational impact assessment, contextual assessment, a series of findings elicited there, and then really integrated for the purposes of the exercise.

The blood safety risk assessment is looking at the probabilities of infectious units, looking at probabilities of filter failure, probabilities of a viremia in the unit. In terms of the budget impact assessment, we looked at, well, how much do we test today, and then we really looked at what potential demand could be under the different options, and especially those options where the indications would be quite narrowed. We looked at operational impacts of this kind of boutique approach. What could the risks be?

Could there be a "pick and pack" error or a labelling error? Could there be a filter failure?

We rated those risks, but we also looked at, well, what's in our environment, what's in our context that will inform us as well. As I mentioned, we have the National Advisory Committee recommendations. We looked at recommendations coming out of SaBTO, which, as I'm sure you know, is standard-setting body in the UK, and their work they have done around the notion that leukocyte reduction is sufficient for -- in this case, they were looking at a medical stem cell transplantation, and that CMV-neg product was only necessary for a very specific and small indication around intrauterine transfusion, neonates, so we looked at that whole environment and did our own analysis across all of these areas to bring all of the relevant data together.

We did the same in the Babesia case, and as I mentioned, we're looking at the present and the future. Currently, in Canada, obviously, the risk is very low. We did our own

seroprevalence study in donors. We surveyed 14,000 donors and got zero positives, and we know that our risk is really rising, the donor travel to endemic areas of the U.S., and that's the key risk factor to our blood supply at this point.

Now, we also looked at the operational impact assessment and looked at availability of testing, whether licensed or not. Obviously, we looked at pathogen reduction technology and the limitations we've already discussed today, and we also looked at that notion of donor travel questions, and although it's a technique we all rely on, I think as Lou mentioned, these questions have limitations, especially for these kinds of pathogens, so that was also called out in our assessment. In terms of contextual assessment, obviously, we need to look more broadly geographically and look at what's happening in the U.S. that has been well described today.

In terms of evaluation, this is where we bring everything together. We bring those assessment results, we bring stakeholder feedback. We do some assessment of risk tolerability analysis, and we really need to

integrate all of that data and understand what are the implications for those risk management options that we had elicited at the outset. I think what's important to know that there's a great deal of work that is done at this stage. We do charts of strengths and weaknesses of the different options. We do risk tolerability checklists. We try to layer in that stakeholder input. But at the end of the day -- I give all that as preamble, because when we telescope that down, we have to have a way of capturing it. So I don't want you to think that, at the end of the day, it becomes only manifest in this small and basic chart. Really what this is is the experts around the table, informed by all of those assessments that I described, really trying to telescope their ideas around safety, around those operational concerns, infrastructure, resources required, and then those contextual concerns around ethics and trust, stakeholder tolerability.

As you can see, so I'll just quickly remind you, so option A here is the status quo. Option B is stopping CMV-neg inventory

altogether. Option C was those two narrowed indications, and then option D was the NAT testing, and option E was the PRT. We really settled on that much narrow indication for making CMV-neg product available and really took that decision in terms of trying to develop our recommendations around it.

What I should also say is that of all the portions of the framework that we've worked so far, this has been the most challenging, and so already there's a new version of how we apply risk tolerability and a new version of this chart that is much expanded in terms of trying to put even more in terms of factors and checklists that help people bring their own judgment, informed by data, to the task of evaluating the options.

In terms of Babesia evaluation, again, it was broken down into two parts, and we really came up with that notion of in the low risk scenario that we would really look at the surveillance data and our own doing periodic donor seroprevalence studies, but then when it came to looking at that future scenario, certainly, our preference, based on the

information we have to-date, was around regional testing, potential with high risk traveler testing, and that was really where we centered our thoughts in terms of what to recommend as we look forward into that scenario as well.

In terms of really moving into the decision stage, this is where we bring all of that integrated data forward, and we make recommendations around which risk management option should we select, and, importantly, what are the implementation considerations, what's the monitoring plan? When will we know that we need to loop back into this process and do a deeper analysis on a given blood safety risk assessment, for example, or when do we need to go and look at changed factors around health economics. So really, it's that monitoring plan that's very important.

Then finally, when the decision is made, then it's reaching back out to that stakeholder community and communicating the decision and constantly keeping that channel open as the issue continues to unfold.

In terms of CMV, what we try to do, we

try to come back and remember the questions that we had set for ourselves at the outset, and you recall that we had asked ourselves around whether the question of proportionality of what we were currently doing and whether it still remained proportional to the risk as we understand it. Really, when we looked at the risk assessments, we concluded that this "belt and suspenders" approach of leukoreduction and also the CMV antibody tested product was really "belt and suspenders" and not needed and that a more restricted inventory of CMV-neg product was a reasonable step to take, and certainly concluded that either option C1 or C2, those narrow and narrower indications for that product, would be acceptable.

So the recommendations were really that we implement that option C2 and that we look at, in terms of implementation, there was feedback that we had received from stakeholders around optimal strategies to provide fresh CMV- negative product for IUT, such as, for example, an inventory that is frozen when fresh and antigen-negative for common antibodies, so

really thinking about the whole picture of what we're trying to do and the change we're trying to make.

As I mentioned, communication and education is, obviously, a key part of our recommendations for this particular issue, and the idea of doing that in collaboration with our National Advisory Committee and the provinces, and making sure that there's not mixed messages going out there in terms of clinical guidelines that might be out already and making sure that there's a common message for clinicians who want to access this product to understand the data and the rationale behind this particular product change.

Finally, the final recommendation, so we've talked about that "belt and suspenders" approach, but the "belt and suspenders" approach never got to the window period, and so now that we've cleared that away, I think there was also recommendation to at least look at the NAT testing platform and really think about the cost-effectiveness and look at outcomes and cost data, and consider whether any change is required

on that score in the future.

Moving then, finally, to the Babesia case study, as I mentioned, the recommendations broke down into scenario 1 and scenario 2, and I really hadn't mentioned already what was recommended there around ongoing passive and active tick monitoring, blood donor seroprevalence studies every 3 to 5 years, depending on tick data, scenario 2 looking at a more regional testing approach.

So that was the recommendation coming into the decision process. The decision-makers put a further clarity around on what would flow from the analysis, and they basically said the seroprevalence study will be no later than 2018, and I think expressed an interest in having a certain period to see for those studies. They also asked that included in the objectives for that donor seroprevalence study that this notion of establishing a trigger to escalate mitigation efforts, so that scenario 2 that I talked about could be studied, and certainly concluding and agreeing that no selective testing at this time based on the current risk was necessary. Just

trying to break down and show that recommendation stage and the ultimate decision stage.

So finally, I'll bring you back to this slide and just with a final encouragement to look at some of the resources and guidance that we've been slowly putting on the site, as well as published articles and case studies as they emerge. We're trying to put specific case studies on the website so that different applications of the framework can be demonstrated, both in the very classic pathogen approach, but in novel approaches in the way that the framework has been used as well. And that concludes my remarks. Thank you.

DR. LEIBY:: Any questions for Judie? All right, if I can, can I have the speakers from the afternoon, along with Roger and Captain Fahie, up here? You should have a nametag where you can find your seat.

Okay, the first question to our panel is, what mitigation strategies are currently available that would lessen the risks associated with transfusion-transmitted HGA, and what are the obstacles to their implementation? Roger,

go ahead. Press the button.

DR. DODD: Oh, okay. I'll take a shot at this, because I've been thinking about it for quite a while here. First of all, I think that we have to figure out what really is the function of this question, because if the function of this question, at this point, is what should we do now, I really don't think it's answerable effectively, because I don't think we have enough information.

Clearly, HGA is the most likely to be of concern of the agents that we've discussed today, but clearly, we really don't know enough else that's going on, so I'll make the assumption that the purpose of this question is to say, if we were going to do a risk-based management process, what would you feed into it in terms of the information here, and I think that that's a reasonable issue. I think that what came to mind, to me, is being things that one could consider as an intervention if you decide to go ahead, so what we should consider as part of the process might, on the one hand, be to encourage industry to develop a test, although I think that it would not be a very attractive target or

perhaps to modify a test so that it could be integrated in a multiplex fashion. I think that most people in this room would probably advocate for pushing for pathogen reduction and seeing the management of this particular agent as a side benefit.

But I'd like, at this point, actually to take us back to the very first opening comments that you made, David, which related to mosquito-borne arboviruses, and ask what was it that drove the very vigorous response to Zika, and I think there's really one major reason, and that was that the outcome of Zika infection is a dread disease, if you will. Nobody wants an infant with microcephaly or brain damage, and that was, in fact, explicitly border bound.

And the other thing was that, although unlikely in the United States, we were seeing the vision of a single pathogen moving in and taking over an entire continent in a matter of less than a year, so this put a great piece of urgency onto it. And these are things that we haven't really asked about these issues, but it does not seem to me, from the discussion of the epidemiology and

biology of these agents, that we're facing a massive, unmanageable outburst of, in fact, any of these agents. So I think that if we were to put this into Judie's process, it would be a very complex issue, but I think these are some of the things that would have to be factored in.

DR. LEIBY:: Thank you, Roger. Lou?

DR. KATZ: Yes, I don't want the question to presume we shouldn't do something, and I think that's an important focus, but my personal belief is that we need to have a discussion about the level of surveillance that we have and whether there's enough potential risk that we need to do surveillance different than we do it now, and that might include going as far as recipient hemovigilance, for example, in some appropriate sample and that sort of thing. I don't think we should do nothing, but I don't think we should do more than discuss how much surveillance we should be doing.

DR. LEIBY:: Ray?

DR. GOODRICH: Well, I think in terms of what are some of the factors that are going to be obstacles to implementation, we'd have to take

into consideration just the fact that with all of these agents, you have seasonalism, regionalism, and those drive some of the economic decision-making factors. Clearly, more has to be known about the impact of the transfusion transmission from the disease standpoint to see whether or not you have (inaudible), and what do I mean by it?

In developing tests, obviously, for something that only occurs where it's only going to be implemented three or four months out of the year, you limit your market. By developing a test that is only used in a certain part of the country for that period of time, you limit it further. You also create a situation in the blood banking community, because blood moves around in this country, where it creates disparities in those who are testing, because they're collecting in regions that are endemic and those who are not, because they're collecting in regions that are not endemic, and that creates a situation that I think it enters into the factors of decision-making about whether or not to do these things.

So as long as you can't define a problem that is big enough from a clinical morbidity or mortality standpoint to warrant that immediate action has to be taken, then it's going to come down to the discussions about seasonalism, regionalism, and how you implement this in a practical way. The comments about we have to encourage companies to do tests I think are interesting because, if it's in their best interest, believe me, you don't have to encourage them to do anything; they're going to do it. So the fact that we have to encourage them to do something must say that there's something that's not in their interest to develop these things, so we have to address that issue and discuss it with them and others in the community, I think, in making a determination as to whether or not these things are going to be implemented. Again, the technologies exist or the know-how exists, but that may not be the deciding factor.

DR. LEIBY:: Susan?

DR. STAMER: Just to summarize, I think I agree with a little bit of what everyone has said. I think the question presumes that we have

to do something more than we're doing now based on 10 transfusion-transmitted infections, so if we did something to change surveillance to have a better understanding. Is that just the tip of the iceberg? Are there more cases that we're not seeing? What is the clinical impact on recipients. I think there's more information we need before we actually say we have to implement an intervention.

DR. LEIBY:: Captain Fahie?

CAPTAIN FAHIE: Yes, I think I have a different perspective on things actually running the DoD blood program. We have roughly about 1.4 million service members in the United States military, about 300,000 of those that are deployed either in harm's way around the world, and one of the things that we have to worry about is the exposure to those individuals around the world, whether they're in Afghanistan, whether they're in Iraq, whether they're here in the U.S., or if they're in the Pacific. As we talk about regionalization and different areas of surveillance and looking at what is there, we always see it all the time, because we always have

to plan for that.

So when we look at stuff as exposure to infectious diseases and emerging diseases, whether it's tick-borne or whether it's viral transmission or whatever, we have to plan for that future and what it would be like around -- what's going to be the next virus that are going to come out there, and what technology's going to be able to eliminate it, although it may not be there. We have to actually look at that ahead of time.

So when we look at PRT or something like that, we're looking at that, because we have cases where we are transfusing emergency whole blood collections that most likely, in a theater, that are not being totally FDA regulated, but what about those viruses that we can eliminate from that if we have to do that.

So those are the kind of things that we actually have to consider when we're looking at technology that we can look at a return on investment for maybe something like that. We had Ebola, we had chikungunya, we have dengue, we have all those different other viruses, and now we have Zika, and as we see, pathogen reduction helps with

that. So, for us, we look at it as we have service members that are being there, we're transfusing you instead of there. Most of the units that we transfuse in a theater, mostly massively transfuse units, so we have to look at what potentially could be in that unit and they're exposed to different places and different countries and different organisms or viruses or pathogens in that country, so we have to really look at that when we look at the technology. We got to look at not only the technology and that return on investment and also the cost.

DR. LEIBY:: Thank you. That's a nice, different perspective from a different point of view. Susan?

DR. STAMER: I just have a question for Roland. In the theater, isn't the other concern, besides emerging infectious diseases, making sure testing for the major known transfusion-transmissible agents is done properly so that you have the comfort to know, even if you can't test for HIV or HBV, you have a technology that eliminates that without the pressure of testing?

CAPTAIN FAHIE: That's correct, and most of the units that we transfuse in a theater are tested before, because we ship here. It takes us about 7.4 days to get blood from here in the U.S. to places like Iraq and Afghanistan, so we can get blood there, we can get products there, but it's actually when that product is exhausted and the shelf inventory is exhausted, that's when we have to go to other means where we actually have to do something to save this soldier's or that service member's life.

DR. LEIBY:: Okay, let's move on to the second question. Under what circumstances would the implementation of multiplex testing technology play an important role in addressing tick-borne infections transmitted via blood donors, and do current circumstances leave stakeholders a position to encourage manufacturers to embrace this approach for tick-borne agents? Katz?

DR. KATZ: Well, I'm going to be cute about it in a sense. If you demonstrate that the risk from HGA or any one of these bugs passes the explicit threshold of risk, I'll be happy to

intervene. The problem is establishing a specific threshold of risk that triggers the response, and that's always been the problem. The definition of tolerable risk is not available, so, I mean, it's like pornography, I know it when I see it sort of thing. I don't think the risk, other than babesiosis, justifies an intervention beyond improved surveillance at this point, but Dr. Epstein may disagree or anybody else in the audience may have a different risk tolerance, and that's the difficult hurdle, I think.

DR. LEIBY:: Roger?

DR. DODD: Well, a question that really hasn't been explored, although the answer was, in a sense, given to us, is we have something like this where's only perhaps a chance of relatively slow, small growth in exposure, and there seemed to be, by and large, effective treatment methods, is it rational to go to the other end of the chain and look at appropriate education of the providers or the transfusers to do surveillance on the recipients and give them appropriate therapy if infected. I think, again, that's

logistically difficult, but it's certainly less of an effort than implementing a lot of additional testing. Well, the next question's about pathogen reduction, but is that a viable approach to consider?

DR. LEIBY:: Well, go ahead. You have --

DR. KATZ: Well, my question to you, Roger, was, tell me a little bit about how you would do recipient surveillance? Would you go to thal clinics and sickle cell clinics with highly transfused cohorts or how would you do that?

DR. DODD: Well, we'll work out the details later, Lou.

DR. LEIBY:: Ray?

DR. GOODRICH: Well, I think one of the important parts, as Lou was saying, understanding where that threshold is. In large part, I think it's very important to understand that, and the presentation that we saw on a model for being able to do this risk assessment, one of the things I like very much about that was the public involvement, because I think the definition in part about whether or not we pass the threshold

has to be determined by what the public believes is the threshold, and in many cases, perception is reality. And so if there is a perception of the issues within the public sector, I think being parts of organizations that have this mission to serve the public interests, I think it's important that we have an understanding of what the concerns are and where that is on their threshold of when action or intervention is required or necessary. So I very much like that ABO model and the approach that was taken or is being taken in Canada of involving the public in some of those discussions about when do we cross that threshold.

DR. LEIBY:: Well, I wonder if, along those lines, if we went up to Massachusetts with Al or Sam or someone else and went to one of these so-called tick talks, where everyone in Massachusetts is checking themselves constantly for ticks, worried about them, if they would have a slightly different viewpoint.

DR. DODD: My guess is that there would be a tremendous push to do something to prevent the transmission of Lyme disease by transfusion,

so you have to be a little careful when you --

DR. LEIBY:: What you ask for.

DR. DODD: -- when you do that.

DR. GOODRICH: But isn't part of that then, Roger, also, as they say, we have to talk to more than just ourselves as a community and informing people that Lyme disease is not transmitted by blood, or at least hasn't been demonstrated to be transmitted by blood so far.

DR. DODD: Oh, I agree, and I'm very much in favor of us getting the stakeholders involved. I think it's not an easy thing to do in this field.

DR. KATZ: I thought that was one of the neatest things about the framework that Judie described, and I thought she would say the phrase I'm going to say, but it is explicitly drives us to a societal perspective, not a siloed perspective, and it is certainly the most important aspect of the framework.

DR. STAMER: I think stakeholder engagement is a very difficult concept to capture accurately. So who do we, in fact, who is the public? Who do we go to for stakeholder

engagement? So to answer the question that you asked Roger about surveillance and recipients, we don't have to do that, but what if there was a program through CDC or CSTE or whatever, depending on your region, to do more tick-borne disease education, especially in blood recipients. So isn't that kind of an intersection of one stakeholder group that we would gather information from, our transfusing physicians, physicians in endemic areas.

When we did the exercise with AABB for Babesia, Al did the stakeholder engagement in Massachusetts, and we did not find that they asked about transfusion-transmitted Lyme, but we got a whole variety of answers, but one of the criticisms was that we went to a very narrow group, it was only in one state, so I think stakeholder engagement is very lofty and noble, and it's a concept that we need to do, because the public certainly should influence what we do and take ownership in what we do, but it's a very difficult concept to get right.

DR. LEIBY:: Okay, why don't we move to the third question. I think we may have answered

this, but I think it's worthwhile addressing, and I think Lou actually had a nice slide on this. Are pathogen reduction strategies a suitable pathway for controlling the risk associated with tick-borne infections and transfusion transmission considering the ongoing emergence of these agents?

DR. STAMER: And we can say the obvious. Of course it is, right?

DR. KATZ: No, I'm not sure it is. I'm not sure I want to pay for that. I come from the wrong background to ask this question. I mean, I had patients with a lethal, epidemic, sexually transmitted disease on waiting lists to get medicines that prevent transmission for years, and I believe that U.S. healthcare is and will approach a zero sum game, and to spend that money on pathogen reduction when we can't get meds to people who clearly should have them, they're a cost savings, and I'm not sure. Will it work? I think it will. Should we spend the money? I'm not positive, and thank God, I've decided it's not my call.

DR. LEIBY:: Ray?

DR. GOODRICH: I think the answer is yes, if you're asking only from the technical perspective, but I think Lou is bringing up the question, and I said it earlier, you've got two fundamental problems. One, this is not a process you do on a small sample of the blood that you then transfuse the rest of the unit. It is something that you do to the blood that you're transfusing, and it changes it. And that has always raised the question and hence the requirement to address those questions about safety and efficacy in clinical performance, and that, in turn -- it's sort of like that story about the stone soup -- that, in turn, has led to the need for us to do large-scale clinical trials, and in order to recoup the costs that are associated with making those kinds of investments, the price of the technology goes through the roof.

So it depends on what you're asking. Will it solve the problem from a technical perspective in preventing transfusion transmission? Absolutely, it will, at least from what I've seen and what I know. Should it be implemented from the standpoint of controlling

it in a way that's reasonable financially, economically, medically? That's the question that I think is still out there, and it depends on a lot of factors that we can't predict today.

I will add one other piece to that, if I could, and that is that I think what's unique about it that has to be taken into consideration is that will it control the risk associated with tick-borne infections, and as I say, I believe that answer is yes, but it does more than that, and when we do these calculations about should we use PRT, for example, in place of CMV screening, the answer might be no, or should we use it in place of tick screening or tick-borne disease screening, the answer might be no, and if we answer it in terms of bacteria alone, the answer might be no, but cumulatively, does that change the answer? That's a question I think we have to ask.

DR. KATZ: I went through the most frustrating experience of my time in transfusion medicine with Canadian Blood Services. We were invited to consult -- we do it every five years -- to try and figure out how much insurance

they should hold, and part of the exercise is they asked us, well, try and tell us if doing pathogen reduction will reduce the cost of our insurance and our liability and all this kind of stuff. And because the assumptions were so -- the confidence intervals on almost all the assumptions were so wide, it was like trying to calculate the likelihood of life elsewhere in the universe. I mean, we just couldn't do it, and so I -- God, I don't know how to answer question three.

DR. LEIBY:: Okay, we'll move to question four then. What mechanisms, i.e., education, funding, regulatory, are needed to increase tick-borne disease research and/or test development, and what concrete actions should follow from today's workshop? I say, I think I've heard one resounding one, which was increased surveillance perhaps, and the other one perhaps was looking at recipients, but I'll let the panel discuss that.

DR. STAMER: Well, I think one of the goals at the beginning of the workshop -- David, I don't know if you said it or Peter Marks said it -- was education, so we clearly communicated

education. Now, unfortunately, the audience was limited, it was limited to us, so how do we continue to promote education? I think education and surveillance are key. I mean, we talked about triggers, we've talked about a gazillion agents today. At what point do any of those agents alone or in combination warrant us to do more? So between education and surveillance, I don't know that there's anything else we can do beyond today.

DR. LEIBY:: Ray?

DR. GOODRICH: I think education absolutely. Being part of Colorado State University, I would say education, but I also believe education is a great equalizer in our society, so having people more involved in the decision-making I think is always a good thing. I would also say it would be worthwhile -- we talked a little bit about this at our sidebar at lunch -- to start thinking about our transfusion policy perhaps in this country from a standardized national perspective, and maybe that doesn't mean a consolidation of the blood industry, but it means a consolidation of the

approaches that we take. Maybe that will require, ultimately, action by Congress, but I really think that until we get to a point where we can begin to consider things solely on the basis, you have this life. As I said in my talk, you have this life-giving, life-sustaining product that is essential. It's as important to community health as a safe and adequate water supply is, and yet we treat it as a commodity and we make decisions on pennies and nickels. So how do we change that perspective, and I think perhaps it requires an elevation to a next level of creating a national policy associated with how we do blood banking and transfusion medicine practice.

DR. LEIBY:: Roger?

DR. DODD: Well, I think there's an issue that's had a lot of discussion and it's perhaps a little bit unexpected, but it's being faced certainly for managing Babesia, and that is how you do manage a partial testing strategy, where you're going to have to increase the amount of resources assigned to a particular product in a particular part of the country or waste a lot

of money doing unnecessary testing, and I don't think anybody's come up with a good solution to this, absent some sort of definitive regulatory reimbursement policy that might be variable.

So there are things that we don't necessarily think about, but if we do think about pushing for and requiring regionalized testing, then I think we have to consider this because of the way that, as Ray points out, blood is collected in this country. It's very hard to deal with that in a competitive environment, even if everybody is not for profit.

DR. LEIBY:: Susan?

DR. STAMER: Roger, even with regionalized testing, however, we still need surveillance, because regional testing is finite, and even though these agents move slowly, maybe not always on the wings of birds, but we need a process for when we know the borders have expanded.

CAPTAIN FAHIE: And I agree with the --

DR. LEIBY:: Go ahead, Roland.

CAPTAIN FAHIE: I agree with the panel members when we talk about education. I think

that's key, educating not only the public, the hospitals, the physicians, even the patients, and sometimes, the politicians, because, for us, that's one of the biggest things. If there's no money in the budget, there's no money in the budget, and that's one of those things.

Convincing those folks that you have to do something is very difficult, and the reason why you need to do something is very difficult, so for us, guidance from the leadership is something that we have to look at, and within our national programs specifically, if there's a standardized policy of how we should be looking at PRT, I think that needs to come forward, because that helps with making sure that we can establish a business practice.

DR. LEIBY:: Al, go ahead.

DR. DEMARIA: I just wanted to comment on stakeholder engagement, which is something I do a lot in terms of a lot of issues, and the difficulty here is who are the stakeholders. We have a good idea who the stakeholders are, but they have no idea of who they are, and the two most important things I learned from the experience

was, number one, we couldn't really define the stakeholders. Most issues, even tick-borne disease, the stakeholders are the people who live among the ticks. If it's HIV, it's the people who are at risk or living with HIV. I mean, all of those things I'm used to dealing with, but for the stakeholders for the blood supply, it was hard to determine, so then you just find sort of ordinary people wherever you can find them, and I found them in Massachusetts, which is not typical of the rest of the country in terms of the perception of risk-related tick-borne disease.

But two interesting things that come out of that, one is no one in the general public has any idea about how blood is collected, distributed, or used. So to be a stakeholder, you have to know where the stakes are, and I think that they all knew that blood was important, they all knew that if they needed it, they wanted it, but they had no context to discussing what donor screening was, so it takes a lot of education around what blood donation is, how blood is screened, what that means.

And then the other most interesting

thing that came out of it, we said, well, there's about 14 million donations in the United States in a year, how much would it cost to do a test for babesiosis, for example, between \$10 and \$20, and somebody said, well, that's only \$140 million, \$280 million, that's rounding off in the healthcare expenditure in this country, why not just test everybody, which it gets to the point of they really don't understand the full context and the marginality and all the things that people in this room worry about, but they have no idea what it is.

DR. GOODRICH: Does that say we're at risk by that fact? I had a thing in my slides about the Mayan civilization, a wonderful civilization. They invented the concept of zero. They invented the concept of the calendar, very complicated. What happened to the Mayan civilization? It completely crumbled and all that knowledge went away. Why? Because they kept the knowledge in only the priestly upper classes of the society. Unless we get broader understanding within the community of some of these issues, I think it will continue to allow

for stagnation, because people either won't know to get engaged because there is an issue, or not to be engaged in the wrong thing because they're thinking of it in the incorrect way. That signifies a problem that needs a resolution.

DR. LEIBY:: Lou?

DR. KATZ: Yes, we're kind of mutating away from tick-borne illnesses into this broader issue of sustainability of the blood supply, and I think that probably almost everybody in this room knows that we're at the beginning stages of discussion about how to deal with that at the level in HHS but outside FDA, and I think FDA unfairly fills a vacuum and makes decisions about risk that might be better dropped on somebody else.

So the risk-based decision-making process could be given to a group like the Advisory Committee on Blood and Tissue Safety and Availability and let the FDA do what they're best at, which is to assess new technologies and assays and devices, and then when we have technologies that will address risk, let a broader group decide whether that's a good approach. And the advisory

committee now has a subcommittee on sustainability, and we're looking at a list of five or six different approaches to maintain a sustainable blood supply, and one of them is as simple as reimbursement reform. You want safety, fine. Pay for it, we'll do anything you want. You want me to test for serum porcelain in a blood donor, I'll do it if it gets paid for.

FDA, by statute, is not allowed to address that issue. So just moving the decision-making to a more broadly-based forum would be good. We talk about a commodity that is available to everybody, how about water, electricity and gas, they're public utilities, they make profit, but there are regional rate-setting boards that say, yeah, well, we want the water supply to be of this quality, then we're going to raise your rates enough to cover the cost of that, and we're not going to let you take more than you ought to have, so all those things are out there floating around in the stew now, and I think these tick-borne agents are a microcosm of that discussion.

DR. LEIBY:: Well, let's use that as a

segue into the last question, which is, for tick-borne agents, does the ABO approach to risk-based decision-making provide a path to prioritizing mitigation strategies? And lastly, are there other considerations not addressed by ABO model that should be included in blood safety decisions? Judie?

DR. BENNETT: Well, of course, I'm going to say that it's an ideal tool to use, but I really do think, at least, it's a way. It's not the only way, but it is a way to look at or compare risk reduction achieved for the resources allocated across a series of pathogens, so prioritizing is a decision driver that could be processed through the framework. It helps you understand notions like opportunity cost. I mean, that seems to be a big issue here that we need to consider.

It gives you a narrative and it helps you to make explicit, all of those factors that you're taking into account when you take that narrative to stakeholders or decision-makers, and just on the notion, if I could just make a comment about stakeholders, let's remember, it's

not just patient groups, ultimately, very important stakeholders, but stakeholders are the patients, the physicians, their funders, their regulators, the public who fund the system, and so I think the framework would help to frame that dialog and that discussion, that narrative, because I agree with what's being said here that risk communication obligations, we don't just satisfy them by doing the circular of information, I really do think we have a more societal role here in making those factors known to the public.

So that kind of leads into the second question, are there other considerations not addressed, and the only thing I would say to that question is, as much as we say in the framework, and this is the premise of the framework, this is societal perspective, what I worry about in this issue is perhaps we need to make that not even just vein to vein, but really from the blood system to the public health system, because it seems to me that there's so much preemptive work that can be done, and maybe most of the investment should be made in the public health system side of things

as opposed to the blood system side of things. Anyway, I'm just saying that it needs to be integrated approach with that societal perspective, and from my point of view.

DR. LEIBY:: Susan?

DR. STAMER: I do think risk-based decision-making is a start. Many of the parameters, like stakeholder engagement, I think need to be better defined, but I think the one thing that is missing is that the framework is best used where there's a national blood system, which we clearly do not have in the U.S., so if we would apply this type of technology in the U.S., we need someone who's going to pay at the end of the day and determine how much there is to pay so we know what we have to work with, because right now, we can come up with the process and a recommendation at the end of the process, but there's still the vacuum of and now, who's going to pay for that.

DR. LEIBY:: Anyone else?

CAPTAIN FAHIE: I think it's a good start. I think it's a good start to actually systematically looking an approach of how you can

evaluate an entire process. I've seen AABB also have a risk-based decision-making process that they have introduced, and it's one way to look at a systematic way of doing things and making sure that you can attest and also defend the decision that you made when you took that risk, so I think that that's a good start, and I think it's something that you can use as something to begin with, so I think it's a good approach.

DR. LEIBY:: Anyone else?

CAPTAIN FAHIE: And for the record, I'm less than 50 years old.

DR. LEIBY:: Okay. On that note, let me summarize quickly what I think we've learned today. First of all, we went into this workshop with it being forward-looking and informational, and I think that's exactly what it was, and that's what it was designed to be. We weren't here to make decisions, we weren't here to say that this agent is the one that we need to have some tests for now, we need to act, it was really to look at what the long-term issues were.

What we did learn quite clearly is that tick-borne agents continue to emerge, their

geographic range expands, particularly in the eastern United States. We learned that deer are the root of all evil. Transfusion transmission of tick-borne agents does occur. There's quite the variety of agents with HGA being the greatest one, at least at this point. They also tend to be highly seasonal, although they occur throughout the year, but certainly, that seems to be a reoccurring theme.

We also saw that older immunocompromised patients may be at greatest risk for infection, naturally, as well as those who are blood recipients. If we want to look at agents and how we want to address them and look for risks, certainly those who have higher titers of the infectious agent in peripheral blood and those with longer durations in the peripheral blood are ones that are probably going to be of greatest concern. We should also be very aware of those in which there seems to be low disease to prevalence ratio, because this may suggest asymptomatic donors that we need to consider.

We spent some time this afternoon talking about mitigation, things like donor

qualification, asking questions; leukoreduction process controls are unlikely to be effective anyway. Testing, much like pathogen reduction, is an option that would likely work. We've seen it with babesiosis, at least in the studies at (inaudible) preventing transfusion-transmitted babesiosis.

But as we went further along, we certainly learned that challenges exist. As Ray pointed out, there's many conflicting influences and outcomes. There's a need in some cases to show a bottom line, and that, in some respects, rides over many of these issues. But I think, in the end, we agree that doing nothing is not an option. So as we look ahead, certainly, there's not enough information at this point, but we much need to consider somethings like surveillance and looking at education as we go forward into tick-borne diseases and understanding the roles they might play. In the end, there are lots of things which we haven't learned, things that we don't know at this point, but those are the challenges that lay ahead for all of us.

So, on behalf of the FDA all the other

sponsors of this meeting, I want to thank you for all coming today. I think it's actually been a great session all day long. The speakers have been excellent. I think these discussions have been great as well, and I thank you, and hope you have a safe journey home.

(Whereupon, at 5:06 p.m., the
PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Carleton J. Anderson, III, notary public in and for the District of Columbia, 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.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: March 31, 2017