accessed. And we plan to work with the Hispanic advocacy groups, both nationally and locally, starting with a survey of the Hispanic communities themselves to find out what they know about Chagas already. And then, also, the healthcare providers that they will actually seek care from, which is not, necessarily mainstream healthcare. It's often local clinics where they are comfortable going for care. We want to reach those people, as well.

In our efforts to educate healthcare providers, we did publish the MMWR in February with the American Red Cross and Blood Systems, basically informing people that the screening has started, and letting it be known that CDC was a resource to be used for clinical questions. We are issuing clinical case management guidance for Chagas Disease, and we hope to have that published in June of this year.

We're going to be presenting at various national medical and public health conferences on Chagas Disease, and there is a

clinical pre-meeting course at the American Society for Tropical Medicine and Hygiene this fall, that is dedicated to Chagas Disease, and is directed at clinicians.

CDC continues to provide clinical support on an individual consultation basis. We are, as I mentioned before, increasing our supply and capacity of anti-parasitic drug. We respond to individual physician and donor inquiries about Chagas Disease; although, to-date, we've only heard from really a handful of the positive donors, or their physicians. And we're working, as Sue had mentioned, with local hospitals in areas where we expect to have a fairly high prevalence of Chagas Disease, to establish Centers of Excellence where physicians have greater familiarity in dealing with this disease.

And, finally, the public health surveillance is challenging because this is not a reportable disease, so any reporting is really on a very volunteer basis. We're hoping to establish strong collaborations between state

health departments and blood banks, so that as blood banks identify positive donors, they can notify the health department. And often, we think, that's going to be the best way to get care for those donors. And we also are very interested in collecting as much data as we can on identified cases of Chagas Disease, so that we can better define the epidemiology, which I think will have implications for screening algorithms, because as you saw from Sue's map, these donors are actually all over the country. They're not only in the south, or only in California, they're everywhere. And that reflects the immigrant population, which is often unrecognized, and has become concentrated in areas that we may not be aware of, that the census isn't picking up, either.

One of the programs that we're very interested in collaborating on is the AABB's biovigilance program, where blood banks will be reporting donors centrally, and that will be, for us, a very welcome source of surveillance data.

We also are going to have the clinical consults that come in to us; although, they're not as many as we would like right now. And, eventually, we expect that this disease will become nationally notifiable.

I just wanted to end with a slide that shows you resources that are available now to learn more about Chagas Disease, and what CDC is doing. We have our web pages. The MMWR is available on the web, and also, our inquiries phone number. We receive inquiries at that number from the donors, from patients, physicians, the press. That is the number to call for the parasitic diseases branch. Thank you.

DR. SIEGAL: Thank you, Dr. Montgomery. Are there any questions for Dr. Montgomery?

DR. GLYNN: I just had a question on the effect of the medications on chronic disease. Can you go over that? And, also, their side effects.

DR. MONTGOMERY: I'm sorry. The effect of the medication on the chronic stage?

DR. GLYNN: Yes.

DR. MONTGOMERY: So when patients are in the asymptomatic indeterminate phase, they are only intermittently parasitemic. However, there is evidence, and it's accepted now, that the parasite is persistent, and that's what causes the progression of the disease.

In the endemic countries of Brazil and Argentina, there have been some clinical trials of treating, they're actually ongoing clinical trials treating patients in the indeterminate phase. And there has been some evidence - these have to be very long-term studies, obviously, to show that the disease progression has been reduced.

Based on that, we are now much more -- our threshold for treatment decisions is much lower. If a patient has - say a blood donor is asymptomatic infection, has come to the U.S. within the last six years, is a 23-year old

person, we would recommend treatment, because of the desire to reduce the progression of the disease. There are no good markers for progression. We can't look at an asymptomatic person in the indeterminate phase and know whether that person will develop cardiac disease or not. But because there's a 30 to 40 percent chance that that person will, we feel that it's worth treating. And based on these clinical trials, we feel there's evidence to support our decisions.

MS. BAKER: Has the CDC started to develop collaboratives with the APHA, the American Public Health Association, and the university-based schools of public health?

DR. MONTGOMERY: We have not gotten there, yet. That will be one of the organizations that we're reaching out to. Right now, we're really trying to get at much more clinical aspects of it. We want to provide education to physicians in a medium that is accessible to them at all levels of healthcare,

but the public health system is next.

We are going to be at the Council of State and Territorial Epidemiologists meeting in June, and that's another effort to reach out to the state health departments.

DR. SIEGAL: Question?

DR. SCHREIBER: CDC has all of these outreach programs now, but what are you doing in the way of surveillance in the community, or epidemiological studies to address what the prevalence and incidents are in the affected communities?

DR. MONTGOMERY: This is an unfunded initiative at CDC right now, so our ability to actively perform surveillance is very limited. However, we are collaborating with several university research studies that are conducting community-based surveillance locally, and one of them will be in Louisiana, we hope. They're in the process of seeking funding now, and then in Los Angeles, there is a clinical-based study where the cardiology service in a public hospital

is screening any patient who comes in for a cardiac workup. That's obviously going -- it's going to be enriched sample. They already have cardiac disease, and it's in high prevalence, we think a high prevalence area, but we are making efforts at that.

DR. SIEGAL: Okay. Thank you, Dr. Montgomery. Let's move on. We're going to first hear from Mike Busch, M.D., who's at the Blood Systems Research Institute, and then from Brian Custer at the same institute, targeted testing for *T. cruzi* in repeat donors.

DR. BUSCH: Thank you. Yes, Brian and I will share this presentation, and the next slide actually outlines. What I'll do is address the first three bullets here. I just want to summarize the studies that we're conducting related to *T. cruzi*, Chagas Disease, both the U.S. activity that is funneling data into Sue, but also, a study that we're conducting under the Red's NHLBI program in Brazil, talk a little about our assessment strategies with current

screen donors in terms of test performance and evaluation, and then also talk about activities we have planned in order to really more rigorously evaluate the clinical status of the identified confirmed positive donors. And then Brian will follow and really get to, I think, the meat of what this committee - one of the issues you'll be addressing, which is whether alternatives to universal screening may be viable, and our approach to generate the data that will help answer that question.

So the first thing, I want to just tell you about a project that's, I think, quite relevant for a number of reasons to the discussion. It's a project that we actually developed two plus years ago, and is now funded, and beginning to move into enrollment phase in Brazil. And it's the Red's program, which this committee has heard about for a long time. For the first time, about a year and a half ago, it initiated an international component that includes a program in Brazil, in collaboration

with our group, as well as a program in China in collaboration with Johns Hopkins. And the Brazil activities include a Chagas study that has three aims. And the first aim is actually to characterize the natural history of *T. cruzi* disease in individuals who are identified as seropositive following a blood donation. And what we've exploited here is the fact that Brazil, of course, has been screening for Chagas for decades, and our close collaborators, our programs in both Sal Paulo, Brazil, as well as in a small region, a region called Minjerass, a small rural region, a city called Santos Claros, they have identified infected donors from about 8 to 10 years ago, and we have samples stored from those donors. So we're actually doing a retrospective natural history study, and recalling donors who were previously identified as confirmed infected almost a decade ago. And then, we're enrolling them now and evaluating the frequency of clinical disease, and also, looking, as I'll explain a little bit later, with fairly

intensive clinical assessments. And also, looking at the evolution of parasitemia, and seroreactivity, and potentially evaluating other potential prognostic markers, especially since we have stored samples from 10 years ago to correlate these potential markers with subsequent disease evolution.

The second aim, actually, is, I think, quite relevant, and I'll show a little bit of data both from studies in Brazil, as well as some of the U.S. data. And this is related to the persistence of reactivity in infected individuals over time. As I'll show you, there are a number of studies, and I'll focus on one, in Brazil, in endemic countries, that have demonstrated that some infected people spontaneously may resolve the parasitemia and sero revert. And when they're treated, and particularly effectively treated, again, sero reversion may occur. And this is kind of a general phenomenon in infections that only establish a transient infection, that antibody

wanes over time. So one consideration is whether some of the borderline reactive problematic samples that Sue has identified that look like they're true confirmed sero reactives, whether these individuals may, in fact, represent resolved infections rather than persistent infections. So one of our aims in Brazil is to correlate the persistence of antibody in these individuals who were historically confirmed positive over time, and correlate that with detectible parasitemia.

And then the third aim addresses another concern, which is, there are several studies, probably not real good ones, but they have alleged that there is a substantial proportion of parasitemic individuals who, in fact, are not antibody positive. In particular, there's one study, for example, from Brazil, where they tested several hundred individuals from a highly endemic region, and identified 10 people who were serologically negative on multiple tests, but were purportedly PCR

positive. The specificity of that PCR assay wasn't well established, so one of our other aims is in the high risk region, the Santos Claros region, is to repeat that study on a larger number of 500 seronegative samples from an endemic region, and see if we can detect any frequency of a cult parasitemia in seronegative individuals.

I want to just take a minute, though, to summarize a fairly recent paper from last year, from a group in Brazil, *Annals of Internal Medicine Study*, publication, and I think it's important in pointing out three or four issues with respect to both the clinical management, and the potential for treatment of infected donors, as well as this issue of sero reversion. And in this project that was actually a randomized, formal randomized trial of Benznidazole, which is one of the Chagas effective agents, and these were individuals who were identified as in the so-called indeterminate phase. They were found through a clinical referral of seropositives,

with subtle, and in some cases more significant cardiac symptoms on exam, but then they were followed for up to 15 years after randomization to treatment or non-treatment. So it's an observation, it gives us the opportunity to look at this phenomenon of loss of antibody, and effectiveness of treatment during chronic phase infection. So I can't even see this from here, but basically, this is the study design. They had about 1,500 people who were referred. The people who were excluded were mostly out of the age range. They wanted to focus on middle aged individuals 30 to 50 years old, who did not have sort of advanced cardiac disease. And then they ended up with a population of eligibles who were then randomized to about 250 per arm, who were then either treated or not treated. And then ended up with a fairly substantial follow-up of again, around -- so there were about 300 per arm, so they had about 283 in each arm who were actually either treated or not treated with Benznidazole.

And, importantly, they were able to document, as Sue kind of alluded to, newer studies are showing that the treatment of people in this chronic asymptomatic phase does result in response that, in this case, this is looking at subsequent progression of cardiac findings using the staging system, I think it's called Kirchner Group Staging of Cardiac Symptoms, so you can see that the treated group had a dramatically lower rate of progressive cardiac symptoms than the untreated group.

This table I particularly wanted to point out, because I think it may be relevant to these borderline reactives. What they found is, this summarizes the outcomes for the treated groups, versus the untreated groups, and then has the odds ratio. And the committee did get this paper. So the observation here is that, again, there was a dramatically lower rate of progression to cardiac disease in the treated group, compared to the untreated, 4 percent versus 14 percent, a lower rate of developing new

EKG abnormalities, 5 percent versus 16 percent. But most important, there was a much higher rate of loss of antibody reactivity, so only 60 percent of the treated group continued to be reactive on three of three serologic assays, and 15 percent completely sero reverted to negative on serological assays following treatment. And even in the untreated group, only 17 percent remained reactive on three assays, and 6 percent sero reverted all assays, so this is further evidence of the sero reversion phenomenon.

And, actually, as I indicated, our aim in Brazil was to study this possibility of sero reversion, and what led us to be concerned that this might be going on was data that we were involved with, with Ortho in the preclinical trial, where we identified, they identified a number of specimens from Latin American countries. And you can see that there the sero reactivity really is quite high, in the range of 3 to 8 signal to cut-off, with some samples in the borderline range. Well, in our initial

screening of our donors in a trial that was a preclinical evaluation, 2 of the 3 reactives were borderline reactive, so this led us to wonder whether we might begin to see as we screen the U.S. donor pool, people who have remote resolved infection who are borderline reactive. Again, so that's part of one of our aims, is to understand that.

Just one other slide to just mention that there are these several existing treatments, drugs that are approved there, not well tolerated, and as you saw, the response rate is not excellent, but I just want to mention that there is a lot of work going on to develop new treatments for Chagas Diseases. Gates Program, for example, is funding development of new drug regimens, and particular protease inhibitors and the concept of cocktail treatments similar to HIV. And the potential of eradication of this organism, I think, is realistic, as evidenced by the natural clearance in some people, and the efficacy of even the Benznidazole alone trial.

So, again, back to our studies, our Brazil study then will enroll 500 donors from Sal Paulo, and Montes Claros who were identified 10 years ago, and matched controls matched by time of positive, time of donation, as well as gender and age, and repeat versus first-time status. And these donors are being, after recruitment, we'll first do a death index search of the potentially eligible donors, which number several thousand, and then we'll recruit working back, working forward from the date of the original donation. We'll repeat all the blood testing, medical history, risk factor assessment, and then they'll have a detailed physical exam, electrocardiogram, and echocardiogram. And we're working with NHLBI cardiology group, which will actually electronically receive the EKG and the echo data, and under code, be characterizing the rate of disease in these previously healthy donors who were now recalled approximately a decade later.

In terms of our own donors, as Sue

summarized, we're contributing data to Sue's summary analysis in the AABB website with respect to reactivity and confirmation data, but we also have, like Sue, developed an IRB-approved protocol, really modeled after her studies, and the clinical trial studies, to enroll and follow these donors, both with symptom and risk factor interview data following the reactive donation. That data is actually elicited from all reactive donors prior to knowing the confirmation status, and then follow-up samples are obtained one to two months later, after the RIPA data is obtained. And those are characterized by the ELISA, by RIPA, and the plan is to do PCR testing using the same modified protocol that David Leiby has described, where samples are actually processed in the field to stabilize the nucleic acids.

And then based on this discussion, we're still unclear as to what level of other organism testing is warranted. And then, importantly, we're hopeful of getting a fairly

large number of these donors really clinically evaluated, similar to what's being done in Brazil. And we actually have an application to Ortho, which is being reviewed, and we're hopeful will support the clinical assessment of at least 50 confirmed positive donors in terms of they can't through their own resources fund the detailed echocardiogram and EKG assessment.

The other activity, then, is to really, as Sue has kind of described, really validate, are the index donation results sufficient to confirm the true infection status, and that will include both validation based on the index data, but also, in correlation with symptoms, but also, importantly, the follow-up findings from donors who do return for follow-up testing, so correlating the index reactivity pattern with the follow-up data.

I mentioned the clinical assessment, so really, just like in Brazil, asking what the relationship is between clinical disease findings after intensive assessment, and the demographics,

the estimated time since infection, which would be when these people left high risk regions, and the findings from PCR.

And one of our goals here is to both characterize the status of a reasonable number of donors, and this would be, again, a collaboration with Red Cross, the resources we hope to get from Ortho could fund clinical evaluations of donors found at Red Cross or other centers. And through that process, our sort of goal is to not only define their status now, but sort of establish a cohort of confirmed sero positive donors who could be followed prospectively, and potentially qualify into treatment trials with some of these newer regimens.

And then in terms of the clinical assessment, the RIPA confirmed donors are the ones who would be eligible for the detailed clinical evaluation that would include the EKG and echo work, just like the Brazil work. And we hope to use the same NHLBI cardiology group to help in the standardized assessment. And, again,

we'll be saving samples, also, that we could help evaluate whether there may be other predictive markers. And there's some evidence that troponin and some other cardiac disease markers may be predictive of clinical disease.

At that point, I'll ask Brian to take over.

DR. CUSTER: Thank you. So I'm going to talk about two things, first, is this idea of the decision analysis study, and I'll come back to that. And then, also, specifically, our experience with these donor health issue questions that we've added to our questionnaires at UBS.

So the aim of this decision analysis study would be to try to say there are potentially different strategies for testing donors, and to look at which ones might be most effective. And, perhaps, also, which ones might be most cost-effective, although, the real goal of the study is not a cost-effective analysis. I will come back to that, so I just wanted to touch

on sort of the other aims of studies we're working on.

Specifically, with respect to the donor health history questionnaire, United Blood Services, for about two years now, we've actually asked race ethnicity questions. In addition, at the time of the initiation of *T. cruzi* testing, we started inquiring about country of birth. And then about a month after we initiated the *T. cruzi* testing, we also implemented three donor history questions. These are, have you spent time that adds up to three or more months in Mexico, Central America, or South America? Has your mother spent time that adds up to three or more months in Mexico, Central America, or South America? And, since your last donation, have you traveled to Mexico, Central America, or South America? And I'm going to show you some early data that we have on this, sort of showing just what the response rates are, and how things are falling in terms of the frequencies.

For each of those three questions,

there are four possible answers. And everybody has, I think, a copy of our health history questionnaire, so you can see that, but those are no, Mexico, Central America, or South America, or (b) for both, being in Mexico, and Central and/or South America. So the results that I'm going to present actually are only for allogeneic eligible donors. We actually, of course, are asking as on all prospective donors, autologous donors, and so on and so forth, but I just wanted to focus on the allogeneic donors at this point. And you can see the date there is from February 26th through April 7th of this year.

So with respect to race ethnicity, this is actually kind of a complex slide in the sense that you can be in different categories, honestly, and there's obviously a Hispanic category, can perhaps fall into some of these other categories. I just wanted to provide that, capturing the capability for getting this information. It potentially could be useful, although, probably not, as a factor for

screening. But you can see sort of the breakdown for the UBS centers.

With respect to country of birth, I want to make a note about this. As you can see, if you look, this is the one that we're having the most trouble capturing the information on, and so we clearly have some work to do here to improve our response rates on this, because we have as much as 30 percent missing here for this. But, obviously, the vast majority of donors are from the U.S., but we do have other percentages from Central America, Mexico, and other countries. The relative number of people who are refusing is small, and there is a distinction between sort of refusing and just missing information.

Moving more directly into the sort of three questions that we're using, we looked at, actually, has the donor spent three or more months in Mexico, Central or South America? This data is broken out by, of course, repeat versus first time status. And you can see the sort of,

for the most part, obviously, most donors haven't spent time in those settings, but we do have distributions of people. The idea here is that one could think about if we wanted to use this as a pre-screening question that would establish whether you would do screening or not, you can look at the various percentages, or the number of people that you might have to screen under certain testing algorithms.

Clearly, like I said before, this is preliminary information, so it's really just sort of to guide you, to just sort of show that we're developing the capability to capture this information right now, and we have some work to do. We're getting pretty good compliance with these questions, but continue to try to encourage people to complete the answers. They are voluntary.

For mother having spent three or more months in Mexico, Central, or South America, the distribution of the data is actually really quite similar to the donors themselves, which I think is, perhaps, not unexpected.

Going on to a donor who has reported travel to Central or South America since the last donation, I do want to make clear that this is not Malaria donors who are excluded for actually travel to Malaria endemic areas are not included here. And one of the important things to recognize is that 5 percent is pretty high, but a number of UBS donor centers, of course, are very near the border, and so there's probably a fair amount of just local cross-border traffic, not necessarily to Malaria endemic areas. So in terms of donor compliance, actually, right now we have 1.7 percent of donors have left these blank. They are voluntary, and you can see that the percentage is about the same for first-time and repeat donors.

Going on, when you think about possibly targeted testing strategies, we sort of look to other examples where they have been sort of some type of segmentation system has been made, and would point out, obviously, CMV testing with separate inventories, West Nile Virus-

specific types of testing. In addition, there are, of course, the emerging issues related to HLA, and considerations about special testing, so we have also implemented questions about ever transfused and ever pregnant on the health history questionnaire. These are used to flag donations that should not be used for plasma components.

Other countries have different approaches to different diseases. In some European countries, there are first-time only targeted for certain infections, and I just point this table out from 2003 data, but just to sort of make the point that certain settings do choose to try to divide the donor population based on specific factors.

All right. So then this decision analysis, at least the way that we've started to formulate, the way that we would look through it, would be, first, we would start with no screening, so as if we were doing nothing, and the purpose of this strategy is really not to say

that that's a viable strategy, that that's what we're here discussing, but what is the benefit for doing the screening, so this is your baseline in which you can compare any results in a model to. And so that's why it becomes critical to include this in the analysis.

You might think of these, as I walk down these slides, actually, it's increasing intensity of testing, and so we're just proposing to sort of take a larger and larger portion of the donor population, and so unlimited strategy might be something like screening of first-time donors, who report travel or lived in Latin America for three or more months. This would exclude screening of repeat donors. I wouldn't say this is a viable strategy. The purpose of it, though, is to try to appreciate what it gains in terms of additional safety, so it's not that this is proposed as one that you would say to BPAC or something like that, that we want you to consider that this is a possible strategy, but I think it's also important to have sort of a

hallmark, kind of test yourselves, are you identifying strategies that are relevant, and what kind of gain would you get from this very limited testing strategy?

Moving on, you could look at screening of all first-time donors and only repeat donors who then reported some kind of travel to Latin America since their last donation. That, perhaps, is a more viable strategy. You could also then, and I think that this is, perhaps, close to where we really are, is after some defined period of sort of universal testing, moving to a regimen where you're then only screening people who present to donate following the implementation, and actually, those who report some sort of travel since that time, or there is the universal screening strategy, which would be just from here on, continue to screen everybody, every donation. I do want to make a point, though, that this is just sort of the ways that we've started to structure the problem. There clearly are probably other

strategies that might be relevant, and we'd be very happy to hear comments or suggestions about how to improve the strategies that we're considering.

So at this point, there are insufficient data for us to really be able to model this. That's partly why we're asking our donors these questions, once we have enough data, and we can actually look at that with respect to also testing results. We'll be in a far better position to see if any of those strategies are really effective, so we stand there.

One of the things I want to make clear is that there's a lot of uncertainty around this, and so we would definitely try to capture that as much as you can in a modeling exercise. And as an example, I wanted to point out, actually, this paper, which was specifically a cost-effectiveness analysis, but it nicely sort of has already gone through a lot of the work of trying to create a mathematical model to talk about Chagas Disease progression, and the various

stages, and so I just show you the model, which, unfortunately, you can't see. But the idea here is that you would need to understand, after having been able to stage the infection, what the probability is that a donor would be in any one of these categories, which, obviously, no disease - that's where most donors are going to be, acute stage - extremely unlikely, indeterminate stage - most likely, versus the chronic stage, where they probably wouldn't pass the donor health history screening. But the purpose of this is also to recognize that Leslie Wilson has done a lot of work already related to this, and she'd be one of our collaborators on this analysis.

And so with that, actually, I would open it up for questions to Mike and I.

DR. KATZ: Brian, that decision model is great as a public health decision model. We're interested, primarily, in not transmitting to recipients. I accept my public health role as a blood banker, and I'm certainly, if and when I identify a Chagas infected donor, going to

immediately refer that person for an appropriate clinical eval. But what we're interested in is transmission from blood components, and my question is, it's a little bit more detail on that aspect of your decision analysis, what kind of data are you going to use to risk of transmission by component X, Y, and Z, and that sort of thing, because that's really what we're about.

DR. CUSTER: I think that's a very good point. I mean, obviously, already we've had the earlier discussion about the predominant role that appears to be of platelet transfusions. That clearly would need to be accounted for. Finding the data, other than platelet transfusions, is a real challenge, but you're absolutely correct, that a good decision model would need to account for the component factors, also. Yes?

DR. KUEHNERT: I just had a couple of questions. One was about the country of birth question, and the compliance rate with that. It

just seemed really low, and I was just trying to understand why that was, compared with your other questions.

DR. CUSTER: It has to do with some operational issues, and it's also a voluntary completion. And I think that is reflects some improvements we need to make within the organization of getting the health historian takers to actually make sure that information is recorded, because I just don't think it's being done right now. So I think it has more to do with some structural issues, than a specific avoidance of that question.

DR. KUEHNERT: And the one that I thought would have the most trouble would be this question about exposure and travel history, and the donor's mother. If you're trying to get at congenital transmission, wouldn't it be - the question would be even more complicated, which I guess, what was the history in your mother before you were born, rather than after. But I guess --

DR. CUSTER: You're absolutely correct, I mean, and so when we thought about versions of the question, as how we would pose it to donors, really that is, indeed, the risk interval that you want to look at, but we thought that that would get too complex, and perhaps not be easy to interpret. And out of fairness to the questions, right now, of course, they haven't been validated themselves, but anything that even is more complex then -- would potentially be more problematic.

DR. KUEHNERT: So that was my final question, was about validation. I mean, how are you going to go about like trying to figure out how a question like this might be comprehended and answered accurately?

DR. CUSTER: It's a good question. I'm sure that we could do some cognitive evaluations. We haven't done that yet. We're really just building the capacity right now to ask the questions, but we do have some more work to do on that.

DR. BUSCH: The mother question is, has your mother in her life resided in these countries for three months, so it would cover back to prior to the donor being born.

DR. KUEHNERT: Oh, right. I was just saying that it also covers a part of her life that wouldn't be relevant.

DR. BUSCH: Oh, I see. Yes, yes. And then the other point, I mean, I think ultimately the validation is the responses, the detection of infected donors, so the question here is once we accrue a year or two of data, and we have 30, 40, 50 confirmed infected donors, were these pre-donation screening questions adequate, because these are not resulting in donor deferral. The donors are allowed to give despite positive answers.

DR. SIEGAL: Dr. Nelson.

DR. NELSON: Yes, I had a question, too, about the validity. As I remember, an earlier study where they looked at donors in Miami and Los Angeles, I think it was a Red Cross

study, and they had controls who answered negative, and they were tested. It was actually one of the controls that was positive. And on repeating the question and re-interviewing the donor, they found that this person actually had lived in Guatemala or somewhere for quite a period of time. It would be possible to validate some of this history. In other words, when a person with independent data, let's say that when a person said that they have or haven't visited there, or they hadn't been born or lived in one of the endemic areas, I mean, that would be possible to do. It would require getting another data set, but I don't know if you thought about that.

DR. SCHREIBER: I think there might be green card issues, or all kinds of things why a person might not want to say that well, I - before they put that wall up, I snuck across the border from Mexico. I mean, there are --

DR. BUSCH: Certainly, the option of doing a parallel follow-up interview of donors

who said yes or no, and I think realistically, our program, as you heard Red Cross, we implemented universal screening, so realistically, to me, the big question, important question will be, are we having any donors who are detected as confirmed positive, who had previously been screened and were negative? Are we having any "incident" cases, or reactors that are detected. And then, particularly, were the questions effective at detecting those infections, because then it would be selective repeat donor screening approach.

DR. SCHREIBER: I think it's a good idea to see if there's some kind of a selection criteria, but are there any other instances where we're doing selective testing? It's easy to do universal testing, and it's easy to use a screening where you get the donors out of the system, but how easy would it be operationally to identify donors who you then only screen that segment of the population, which could be 4 or 5 percent, say, or 3 percent.

DR. BUSCH: What we do, for example, with CMV, if a donor is historically CMV negative, they're the subset that get tested. For West Nile, we literally track zip codes, regions, and are able to then selectively do individual donation NAT on regional donations that come from zip codes that are literally sticker coded, as from a particular subset of a larger region. So these are responses to the need to try to operationalize. One of the ultimate goals would be to have clearly, it's as Sue said, it's the implementation of selective testing that makes these approaches somewhat problematic. But those are solutions that can be solved, they're really IT, and bar code labeling solutions that we think if there's opportunities to overall save resources by this kind of approach, we can fix those problems, and safely triage samples that need question-based selections.

DR. FINNEGAN: One of the things that's been concerning me as we're talking about

very small numbers, out of a very large group of people. We're also talking about cost effectiveness for lots of areas of the country that don't have the funds to do universal testing. And it seems to me, we're also talking about a blood supply that's going to be narrowed, and narrowed, and narrowed as we test for more, and more, and more things. And according to the Red Cross study, it would appear that if the patient is not in parasitemia, that, in fact, perhaps the blood is not at risk. And so my question is for your Brazilian partners, is anyone looking at a test for parasitemia?

DR. BUSCH: Yes, not as a realistic alternative to screening. I mean, there, because they've had such real epidemic activity, they do three tests in parallel, historically, serologic for antibody. And I'm not aware of any success. I mean, the problem is the parasitemia is so low-level, I mean, what Sue sort of didn't point out, the method, such as David developed, use 30 milliliters of blood, and you lie a single

parasite in that 30 Mls would release this repeated kinetoplast sequence, so to take 30 Mls and process it through, it's not like NAT that we do for the other viruses where it's a half Mil of plasma. It's just unrealistic. Parasitemia is so low and intermittent that I don't think you could rely on a negative nucleic acid test to assure non-infectivity.

DR. SIEGAL: Okay. Dr. Katz, and that'll be it, because it's time for --

DR. KATZ: Yes. I have a question about travel and Chagas Disease. Lou Kirchhoff, an old pal of mine from Iowa City says he's unaware of a traveler to Latin America acquiring Chagas Disease in what constitutes the bulk of travel from the United States, so I'm very interested, and maybe Sue Montgomery can shed some light on this. How non-specific is travel going to be?

DR. BUSCH: Those Canadian cases where Canadian citizens who lived --

DR. KATZ: Lived, yes.

DR. BUSCH: But how do you define travel?

DR. KATZ: Yes, I think that's what I was asking, how do you define travel?

DR. CUSTER: Well, of course, so we're leaving that as just sort of three or more months, and that's not necessarily saying travel. But, obviously, it could be three months, or it could be 10 years.

DR. SIEGAL: Thank you very much. Shall we take a 10-minute, rather than a 15-minute break so we're more on time? So everybody back by 25 of.

(Whereupon, the proceedings went off the record at 4:26:07 p.m., and went back on the record at 4:39:37 p.m.)

MR. JEHN: Okay. Could everybody please take your seats? We're going to go ahead and get started. Next on the agenda will be the open public hearing. I believe the Chair has a statement to read prior to that.

(Audio problem.)

DR. SIEGAL: -- a particular matters meeting, and now I'm required to read this to the group. "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If

you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking." So, thank you.

We have five speakers, they will have five minutes each, including questions. So the first speaker will be Dr. Benedict Marchlewicz from Abbott Laboratories, Abbott Diagnostics. I hope I pronounced you correctly.

DR. MARCHLEWICZ: Thank you very much. Again, I am from Abbott Laboratories. I am the program manager for PRISM R&D, and I'd like to thank the committee and CBER for allowing us this opportunity to present some information today on some assays under current development at Abbott.

We'll be talking about two assays that are currently in development at Abbott. One is a PRISM Chagas assay. Those who may be familiar with the PRISM system, is a fully automated chemiluminescent screening assay, where you have several other markers already on the

system. And along with that, we are developing a Chagas confirmatory assay which is an immuno blot assay which I'll describe later.

A key part to the design of both assays for Abbott to try and address some of the issues discussed previously this afternoon relative to lysate-based assays were there may be cross-reactivity due to the nature of the substrate being used. Abbott is approaching this with a recombinant based peptides for both systems. And you'll see that this from some of the data that we've generated minimizes the potential for cross-reactivity, with some of the other parasitic diseases mentioned so far.

For the PRISM system, to give a quick overview of how the assay is formatted, the patient sample is incubated in it's specimen diluent, with micro particles coated with the specific recombinant antigens. After appropriate incubation time, it is washed to remove unbound antibody. The micro particles are then incubated with a mouse anti-human conjugate that is linked

with an acridinium dye, after again the appropriate incubation and wash, an activator solution is added. For those samples that are positive for antibodies to *T. cruzi*, there is release of light. The acridinium reacts with the activator to produce photons of light. The amount of light released is proportional to the level of anti-*T. Cruzi* antibody in the specimen.

The four peptides that we use in our system, just to give a very brief overview, we have designated as TcF, FP3, FP6, and FP10. This gives you an overview of just the raw four amino acid size and molecular weight. In each of these, we have repeat sequences primarily of the Pep-2, which are specific to the two most vegetative disease states of the *T. cruzi* organism.

As we've heard already today, specificity for a blood screening product is really crucial. This is very preliminary data on approximately 12,000 samples looking at the specificity of the PRISM Chagas assay. The

majority of these specimens were collected from areas where we have seen in some of the previous presentations that the incidence appears to be higher within the U.S. These are all U.S. source samples, so the values are certainly within range of what Dr. Stramer had shown of the .04, .042 reactive rate.

Also, the fact we are identifying some confirmed positives, and by confirmed, I mean they've been tested by a RIPA test to show that there are positivity in these areas where the samples are collected.

Another key point presented earlier today was the cross-reactivity with some of the existing methodologies, especially with Leishmania samples, and malaria samples. To-date, we have tested over 40 Leishmania from the visceral and the cutaneous stage of the disease, sourced from India, an endemic area for Leishmania, and we do not see any cross-reactivity. All the tests have come up negative. Similarly, 10 malarial samples have been tested

and all 10 are negative.

In addition to the specificity, certainly for a blood screening assay, sensitivity is extremely important. We have looked at over 400 confirmed positive samples. Again, the confirmed positivity is based on RIPA testing. All of these have been sourced from endemic areas in Central and South America. All 419 specimens are repeatedly reactive in the PRISM system.

The other part of the story we've really been hearing a lot about is beyond the screening test. There's the need for some form of supplemental testing, so we are developing in parallel to the PRISM screening system, and immuno blot confirmatory assay. This figure shows the configuration of the immuno blot. We have designed it with three on-board controls. There is a high IgG control and a low IgG control, which is, in essence, the cut-off for the assay. We'll talk about interpretation in a minute.

There's also an on-board sample control, and anti-human IgG to show that it's coming. Then we have the four peptide antigens.

In the interest of time, we'll go through the actual mechanics, but very similar to any other immuno assay. For the interpretation, as I mentioned, the low on-board control is defined as a one plus. Any specimen that develops two or more bands with at least one band exhibiting a one plus reactivity, is determined to be positive for antibodies to *T. cruzi*.

Sensitivity of the confirmatory assay is important, so we've looked at, again, over 400 specimens that are RIPA positive, all 410 were immuno blot positive with no discordant results. Those samples have been sourced from a number of endemic areas covering what we've looked at in terms of Central and South America. Although the specificity is -- we're looking at positive reactives in a confirmatory assay, we've also looked at 500 unscreened random donors. All of those are negative by both RIPA and Chagas in

PRISM. And lastly, we wanted to look at unrelated medical conditions; meaning, other viral disease, autoimmune diseases. All of those were negative, unless confirmed also by RIPA and immuno blot. Similar to the PRISM assay, the specificity was looked at on Leishmania, and malarial samples, again, 100 percent specificity, no false reactives with the confirmatory test on those parasitic infections. So, in summary, just wanted to highlight for the committee that there are other alternatives in development, a fully automated blood screening assay for *Trypanosoma cruzi* on the PRISM system, as well as what will be a licensed immuno blot confirmatory assay that will be performed on repeatedly reactive specimens in the PRISM system. Thank you very much.

DR. SIEGAL: Thank you, Dr. Marchlewicz. The next we're going to hear from is Dr. Brian McDonough, Vice President for Donor Screening of Ortho Clinical Diagnostics.

DR. McDONOUGH: Yes. As I have no

slides, I'll speak from this microphone, if that's appropriate. I am an employee of Ortho Clinical Diagnostics. I simply want to take about a minute to provide you with some additional background information.

If we use the denominator of 16 million as the number of annual donations made in the United States, or 1.33 million per month, then based on our data, which includes shipments, as well as contracts with testing laboratories, we can confirm that as of the end of April, 71 percent of the U.S. blood supply will have been screened on a monthly basis. And through the end of May, that number will be 77 percent. The existing laboratories that are now doing testing have more than enough capacity to test the additional 25 plus percent. In addition to that, we have the capacity to install our system in up to 30 different sites.

Lastly, I would like to say that we will be filing our 510(k) application on the first of August of this year, and we expect our

cadaveric claim to be filed on the first of December of this year. Thank you.

DR. SIEGAL: Thank you. Next we're going to hear from Celso Bianco of the ABC. Dr. Bianco.

DR. BIANCO: Thank you, Fred. I'm a full-time employee of America's Blood Centers. I was born in Brazil, a conflict of interest.

(Laughter.)

DR. BIANCO: But I'm a citizen of the United States. I'm representing 77 members of America's Blood Centers. They provide about half of the blood supply in the U.S., and we have also two Canadian members, Hema-Quebec, and Canadia Blood Systems.

We heard a very good review today of many of the issues, and some of the data that is coming up. And I'd like to give you a very short overview of the status of implementation of the Ortho assay among members of America's Blood Centers. And explain why some of the ABC members do not have a sense of urgency about implementing

the assay. And, finally, ask that the committee discuss and advise FDA about the number of issues that are very important for us. Regarding the status of implementation, about 35 percent of the ABC member centers have implemented the assay, or have out-sourced testing to contract laboratories that are performing the assay. This represents about 3.6 million of the 8 million collections by ABC member centers in the United States.

Another 20 percent, about 2 million, are anticipating implementing testing during the current quarter; that is, by the end of the second quarter of 2007. About 35 percent of ABC members are waiting for one of the following; outcomes of the studies at Blood Systems and the American Red Cross about the prevalence of confirmed positives, geographic distribution, correlation with answers to questions about risk of exposure to *T. cruzi*, and most importantly, the results of look-back tracings of prior donations. And the other part of this group are

waiting for availability of the Abbott test, because that's their main testing platform. And they do not want to add a different, second platform. And, at the end, we have about 10 percent of our members that have said that they plan to wait until the FDA issues a mandate before they implement the test.

The low sense of urgency about implementation derives from a number of factors. First, the limited number of transmissions of Chagas disease that we heard, the seven cases in about 20 years. And the fact that, actually, despite the fact that studies have demonstrated a number of positives, particularly, the Red Cross studies, in certain areas of the country. We would expect more transmissions.

The second concern that they have are the negative results in the 40,000 specimens of the Ortho pivotal trials, and the fact that FDA required extension of the trials to generate confirmed positive results, as shown in the presentation very clearly today by Dr. Susan

Stramer.

The other issue that concerns those members is what I called here lower specificity of this Ortho assay, but I was told by Dr. Hira Nakhasi is that this is low positive predictive value, and he gave me a hard time about it. And of the data that was posted at the AABB website earlier this week, there were 41 of 332 - no, I think that there is an error here - there were 212, that's a copy that has an error, that it was about 20 percent of the specimens that were confirmed by RIPA, so 80 percent were not confirmed, the positive predictive value is about 20 percent.

And, finally, the question of no confirmatory test, no additional supplemental, more specific test. And I say here that Ortho had not indicated that it did not intend to submit RIPA for licensure. And I was told today, I was corrected that the Ortho is still considering analyzing the data, is still considering implementation of the test.

Finally, we hope that BPAC will provide advice to the agency on a number of issues that are very important for us in the blood banking community. Blood Systems introduced the assay, and additional donor questions in a pilot to help define the most appropriate format of future donor screening for *T. cruzi*. And this is the model aptly presented by Drs. Busch and Custer.

We expect that -- we will also consider this early testing a pilot, collect and analyze the accumulated experience in order to generate policy. We hope that BPAC will consider and advise FDA on the merits of the different approaches for screening, including screening for selective screening, or these different formats that were discussed here today.

In one of the bullets in this point, I added that screening for tissues and organ donors, particularly organ donors, since they are being infused into severely immuno compromised patients, should be considered. I received a

comment from a member of UNOS, Dr. Michael Hagan, indicating at this point, that they are not prepared yet to introduce screening for Chagas, because they do not have a system that can, in terms of logistics, have the assays available as they are needed with the speed and 24-hour, seven days a week that is required for transplants, organ transplants, particularly.

And we also hope that this concept of selective screening will be discussed today, and will be accepted, because unless this moves on, there will be no encouragement for the development of the logistics and software that are necessary for a successful implementation of a selective screening program.

We hope that there will be encouragement for alternate manufacturers. We know that if this is proven to be a very important test for blood safety, that it's essential for blood safety, that we have more than a single manufacturer.

And, finally, we hope that there will

be encouragement for the development of licensed confirmatory assays, or algorithms based on validated, but yet unlicenced assays. And I thank the committee for the opportunity to make these comments. Thank you.

DR. SIEGAL: Thank you, Dr. Bianco. Next we'll hear from Scott Brubaker, Chief Policy Officer, AATB.

MR. BRUBAKER: Thank you, and I'd like to thank Mr. Jehn for accepting our request to be invited to present. I do have a conflict. I work full-time for the AATB. I'm Chief Policy Officer, and I'm Office Liaison for a few of our committees, and many of our task forces.

I'm going to talk a little bit about process conventional HCTPs, conventional is a term that FDA actually gave to us in one of their rules, final rules. I think it was the DTP rule. Our tissue banks were called conventional, so we've stuck with that term, and I'll use that throughout the presentation.

A little bit of history about AATB.

I won't go through that due to limited time, but we do represent now about 100 accredited tissue banks. There are about 25,000 tissue donors annually, per our surveys. And I think with Dr. Stramer's information, that would equate to possibly one, maybe two tissue donors a year that would be positive for Chagas.

Now the conventional HCTPs on the FDA list, those are the ones that would apply to us, and the arrow, I've rearranged the order, but the arrow is indicating distribution from high to low. And bone is actually very high compared to the rest of the tissues, and I'll show you that on graph.

AATB has different designations over the years. Since 1976 they've evolved, and you can see those there. We also cover reproductive tissues and have standards for those, and accredit those banks. We accredit about 10 of those right now.

So this is one of the graphs I wanted to show you that does have musculoskeletal

allografts and distribution back from 1996 through a few years to 2003. We're currently putting together a survey to cover the last three years, and we'll update this, but you can see for musculoskeletal tissues, which includes bone and soft tissue, we were at about 1.3 million in 2003, and of those 1.3 million, there are about 81,000 soft tissue grafts included in that number. And if you look at that broken down, you can see those are pericardium, fascia lata, ligaments and tendons in increasing numbers of distribution.

It's important to keep in mind a little bit about the different types of tissues that conventional tissues do cover. And just to give you an idea of how musculoskeletal grafts are handled, they're recovered aseptically and either kept refrigerated or they're frozen soon thereafter, within three days. If they're kept at processing, they're kept refrigerated. They're usually just cleaned and disinfected, and kept refrigerated, and I'll go over later in

another slide how long they are refrigerated.

If they're frozen, the processing can occur months later. They'll be thawed, cleaned, disinfected, and often sterilized today. Sometimes before thawing, depending on preprocessing cultures that were usually obtained at recovery, there can be a non-terminal gamma irradiation if it's indicated because of the organisms that grew. But after thawing, there are chemical washes and soaks. It can include alcohols, detergents, surfactants, hydrogen peroxide. Today, now, the processing includes agitation, sonication, centrifugation to really remove the marrow elements and lipids from the interior of the bone.

Now, possibly, in many of the grafts, musculoskeletal grafts that are distributed today for bone are demineralized, and that's using a very strong acid, many washes and soaks with that acid, and then it's buffered to come back to a normal pH. Now following that, the grafts can be very often lyophilized, which involves another

freezing process down to negative 80 degrees Centigrade. And the residual moisture content, in our standards it must meet less than 6 percent, so many organisms or microorganisms cannot survive that kind of reduction in residual moisture and survive. Parasites definitely cannot.

Freezing or cryo-preservation can occur, as well. And there's often now today, with ligaments and tendons, used for sports medicine applications, a terminal gamma irradiation that occurs, and you can see it's 1 to 2.5 megarads, which is equivalent to 10-25 kilogray doses.

Now I thought one of the most important things I could do would be to show you pictures. These are demineralized and lyophilized bone products. As you can see, they come in different shapes, different sizes, and configurations here. This is demineralized bone, black powder that's widely distributed, and this is an injectable paste. It can be even twisted,

and shaped and formed. This is a putty-type. Then we have what we call our traditional grafts, which have been used for many, many years in different applications, corticocancellous, this is just cancellous blocks. These are ilium strips, and these are not doctored pictures, these are exactly how they looked to the clinical as he or she is implanting them. This is an illia crest wedge, or a tricorticol wedge, and this is a patella wedge.

Now sometimes the bone can also, after going through that processing, pieces of the bone be put together. Actually, it's a lot like carpentry when you think about it. There are these -- you can't see these dowels here in this graft, but they are made from cortical bone, and they're holding cortical and cancellous bone together. Very strong grafts are produced this way. But you can see, again, that there are no marrow elements or lipids left.

Now grafts can also be determined fresh, frozen, cryo preserved, or lyophilized.

And a lot of these, especially this graft, which is a patella ligament, often called a bone tendon bone, and this Achilles tendon graft, they are often irradiated at the end of the processing today so they can be labeled as sterile.

Now this is the only picture that doesn't represent what the surgeon sees at implant. It's to show you the joint of an ankle, but fresh osteochondral grafts are also offered, and the most high uses of the knee. Next is the ankle, then the shoulder, and it's rare for the elbow for reconstructions.

Normally there would be a lot more connective tissue, that's part of that graft and the capsule is in tact. Now for skin, it's very interesting, it has changed over the past 10 years, fresh skin is rarely distributed, but just by a few banks and in low numbers. Cryopreserved is next in line, and much higher than fresh. And this is a piece of mesh skin used for burn patients, so that's pretty much what that looks like, but they are mostly cryopreserved.

Then we get into the rare lyophilized skin grafts, which in the U.S. is not very popular any longer, but this is the most popular type of processing in skin today, and mainly by one tissue bank. But it's decellularized freeze dried matrix, and there's a picture, a depiction of it those ways. And then this can also be cryofractured into an injectable form and used for different various applications. So a lot of processing, even for skin, that occurs.

Now we get into cardiac and vascular. Basically, they're just infected grafts subjected to antibiotics, and cryopreserved, and you can see the different types there. So this is the one we're concerned about, and AATB has had standards since 2001. We've required heart valve donors be evaluated for Chagas risk. Banks have been doing it by questionnaire. When they recognize a risk, then they usually test, and they do that on their own. But that is, a myocardium is a risk tissue, and the processing method is a risk, as well.

So here's the different methods of preserving and storing. I just wanted to show you the one for frozen, and there was a question about the temperatures, and how long. But normally, it's below negative 40 for long-term use is what's commonly used the most, because it does allow the longest time for storage.

Now parasites can be preserved by refrigeration, preserved by cryopreservation, killed by these other three methods, and I could probably put demineralization in there with the acid washes that are done, so a majority of the tissue types that we do distribute, our banks distribute, would be able to kill the parasite.

Now this isn't in your handout, but there was a question about does irradiation kill parasites? And this was a paper that was actually published in 2001, and they looked at malaria parasite in blood, and would the 15 kilogray sterilization dose in the UK kill the malaria parasite for tissue, and the determination was yes, it would. It would be

very safe. In fact, a much lower dose of 574 grays would kill Plasmodium falciparum. And there was just a graft.

So to finalize this consideration, we hope that this does continue to be a tiered risk-based approach for our conventional HCTPs, when you're considering testing recommendations. This was actually promoted by FDA, that they would do this type of tiered risk-based approach in their publications going back to 1997.

What we'd like to do is, there's many validations involved with our processing methodologies that are in place today, and we'd like to discuss that more with FDA, and we have actually done that. And maybe we could have a workshop and they could better understand our processing and validation methods.

We do have a high false positive rate for cadaveric specimens, historically, so we'd like to work on that. And that's all, thank you.

DR. SIEGAL: Okay. Thank you, Dr. Brubaker. The last is Linda Fraser, Executive

Director, Rochester Eye and Human Parts Bank, New York.

MS. FRASER: Good afternoon. I have no financial interest to declare; however, I am Director of an Eye and Tissue Bank in Rochester, New York, and I currently serve on the Eye Bank Association of America's Medical Advisory Board, the Accreditation Board, and the Board of Directors as Secretary of the Association.

On behalf of the EBAA, thank you for allowing me the opportunity to speak this afternoon, and present an EBAA perspective on eye banking and corneal transplantation, as it relates to Chagas disease. I'm pleased to present this perspective. All of you should have a full text of my comments. I'm only going to highlight those for you.

The EBAA was formed in 1961, and represents more than 98 percent of the eye banks in the United States. Medical standards were promulgated in 1981, and are based on scientific research, and information that relates

specifically to eye banking and corneal transplantation. EBAA standards are reviewed semi-annually, and are updated to ensure state-of-the-art practices.

The Medical Advisory Board has instituted a number of firsts in the field of transplantation, beginning in 1986 with HIV testing. Subsequently, instituted hepatitis B and hepatitis C testing. In 1991, we introduced an adverse reaction reporting system, and data have been reported since then, and made available to the FDA, among others. These contributions have created a system that's universally recognized as safe and effective.

Since the inception of our medical standards, there have been no reported fatalities as a result of corneal transplant, and since 1987, there's been no transmission of systemic infectious disease as a result of cornea transplants.

To date, there's been no reported transmission of *T. cruzi* via cornea

transplantation, or transplantation of other ocular tissue. In fact, in the one known case in which a cornea was transplanted from an antibody positive donor in May of 2006, the transplant recipient is disease-free. The transplant surgeon was appropriately advised, and no adverse reaction has been reported. Additionally, the CDC examined the other cornea which had not yet been transplanted from the same infected donor, and reported finding no evidence of *T. cruzi*.

We know that during the acute phase of Chagas, shortly following vector borne transmission, active and localized ocular inflammation occurs. This active and localized inflammation is easily detectible during physical assessment, which is required, and would make the donor's ocular tissue ineligible transplant according to our current standards.

When the disease enter chronic phase, visible ocular inflammation does subside, but if active lesions like keratitis were present in the

corneas in the chronic phase, the lesions would be identifiable on slit lamp inspection of the tissue; thereby, again, rendering the ocular tissue not eligible for transplant.

Having said this, during the chronic phase of the disease, ocular inflammation may not be detected, and thus, not identified during physical inspection of the eye. It might be considered eligible for transplantation, initially. However, this group of infected donors likely would not provide ocular tissue for transplantation, as they would likely be eliminated from the donor pool following review of the medical, social, and behavioral risk assessment, and medical record.

This review is conducted by eye banks, and may find a potential donor with Chagas disease ineligible at two separate points. Number one, the conditions may be documented in the donor's medical record as Chagas, or suggestive enough to determine a rule-out. Number two, the travel record of the donor may

also point to suspected Chagas exposure, and this information would be considered in conjunction with other supporting information, and medical record material.

There have been no reports of *T. cruzi* organisms isolated from the corneas or ocular tissues of human patients in the chronic phase of Chagas. We're not aware of any research demonstrating the presence of live organisms in human corneal tissue. Ocular lesions in the chronic phase of Chagas are primarily limited to post inflammatory or immunological changes in the retinal pigment epithelium in a small percentage of affected patients.

Previous speakers have spoken about research and animal models, and I won't repeat that, except to say that in summary, there's no evidence that infectivity in these animals or via these routes of inoculation, or with these numbers of organisms, mimics clinical infection in humans.

Beyond the issue of whether the

pathogens can remain viable in the human cornea, are the issues of whether they're transmissible via cornea transplantation, and whether any resulting disease in the recipient poses a significant threat to health, reference the previous case that I discussed.

Given that there are no reported cases of transmission through corneal or ocular tissue transplantation, and that active screening policies are employed that can help to identify the disease, the EBAA would not support mandatory serological testing for *T. cruzi* for eye donors at this time. It appears that the risk of transmission of Chagas via corneal transplantation is low enough to make routine testing of corneal donors for Chagas unlikely to prevent a single case of transmission. Serological testing should not be required or recommended for eye donors unless data specific to ocular tissue proves that such a step would provide statistically significant measure of protection. Otherwise, Chagas should not be

considered a relevant communicable disease for ocular transplantation purposes.

In determining a testing requirement, the cost of the test, the number of potential lost, otherwise usable tissues due to false positive results should be considered. And, in addition, the lack of an approved test for cadaveric samples is an impediment to establishment of a requirement or recommendation at this time.

In summary, we believe that it's counterproductive to test for Chagas disease for ocular tissue. We can safely say that the risk of transmission via corneal transplant is reasonably estimated to be extremely low, since recipients are not immunocompromised, as organ donors are - I'm sorry - as organ recipients are.

Moreover, should Chagas disease ever be transmitted via ocular tissue, it's very likely that it would be treatable, as the mortality rate from the disease is also known to be very low. In the absence of evidence for

transmissibility of the disease via ocular tissue, we would urge the FDA to collect adequate relevant data on which to make an informed decision. Screening through physical inspection of the eye and its parts, the medical, social, behavioral risk assessment questions, and review of medical records are all tools in a complete donor profile that we evaluate for tissue suitability, and that would appear sufficiently to reduce the risk of transmission of Chagas disease through avascular corneal tissue. Thank you, again.

DR. SIEGAL: Okay. At this point, unless there are any other speakers who wish to be heard, we will proceed to the open committee discussion with questions for the committee.

DR. DUNCAN: So we'll begin with the blood screening part of this question, and that specific question is - "Please comment on any scientific issues that FDA would further consider in developing its recommendations on implementation of blood donor screening for

antibodies to *T. cruzi*."

DR. SIEGAL: Anybody want to start?

DR. KATZ: I will. I think the critical issue is, unlike HBV, HIV, HCV, where we understand that a large majority of infected donors transmit to recipients, and we do understand that in Latin America where this disease is endemic, and transfusion practices are different, and screening assays they're using are different, whole blood and platelets clearly transmit with reasonable frequency. We transmit - I think this is going to be a right number - 4 million doses of platelets annually, approximately, in the United States, but closer to 14 million of red cells. Virtually, none of that, very, very little is whole blood, so I think my biggest question at this point is how much transmission is going on, apart from how many donors have confirmed antibody? And is this an opportunity where both the regulated community and the FDA can have an interval here prior to the definitive guidance coming, whenever that

comes, when we can think out of the box a little bit about a risk assessment approach that is a little less blunt than universal screening at all times.

DR. Di BISCEGLIE: I guess in terms of scientific issues, we've really heard very little about an issue that I think is important, which is the correlation of the screening test result with parasitemia and infectivity. We've heard little bits and pieces of it, but I'm not sure we need to wait for that before making a decision, or the agency should wait for that before making a decision to implement screening of whatever form. But that's something that clearly needs more work. Maybe we just didn't hear about it today and the data exists, or maybe the data need to be gathered.

DR. NELSON: I'm impressed that this screening test, the Ortho test, and probably the Abbott, as well, seems to be pretty good. There were only 150 out of a million, so we're not going to have -- and 20 percent or so of those

were confirmed with a confirmatory assay. And that doesn't sound good, but it's pretty good, it's better than the other tests that we're doing. And this is not an insignificant disease, 30 percent of people go on to chronic cardiac or GI symptoms, so I would think that from the data we have, I can't see any rationale for not implementing screening. Now whether we implement it for all donors, or a selected subset of donors, or selected those who have platelets, but I can't see any reason for not implementing screening given the data that we have now.

DR. FINNEGAN: I'm going to follow that up with a classic orthopedic comment. We have the technology, but we have no good reason to use it, whatsoever. I think the -- that's a little caustic, and I don't mean it to be that caustic, but if you look at the look-backs, I mean, that's pretty impressive that we weren't screening. We did all these look-backs, and we have no transmission of disease. And I agree that the disease is not a good disease to get,

but it seems to me, and I agree with Adrian, that perhaps we're not testing for the right thing. Perhaps we should be testing for those patients who are in the middle of a parasitemia where they could, in fact, infect someone, rather than whether they have the potential to ever be infected.

I do think it's a good public health screening test, and that it does pick up those people who come here who have the disease. But I think for the -- if you look for the cost -- I mean, I'm in a big public hospital with its own blood bank, and that cost is going to be significant for the system. And the question is -- and I'm in a state where it's a disease that probably we need to worry about. The question is, is it going to be -- is a cost-risk benefit ratio good, and I think the answer is no.

DR. NELSON: I disagree.

DR. DUNCAN: If I could just insert one correction. You cited that the look-backs are all -- I mean, there are no transmissions on

look-back, and that's not exactly right. There are a lot of look-backs where there's no sero positivity, but there are five out of 13 that were positive.

DR. FINNEGAN: Right, but the test that the American Red Cross just did, there are none out of 30 whatever she gave.

DR. SIEGAL: I'd like to ask, if I may, if there's any way of comparing the transmissibility in a country where there's indigenous transmission, as compared to a country like our's in which there is no real transmission from vectors, so if we have anything to do with the situation, as we do in AIDS, it's the primary infections which are the highest transmitters, and that might be something that might create much more trouble in South and Central America, than in the United States. Is there anybody who's studied that, has looked at the differences?

DR. DUNCAN: You mean looking at the difference in the probability of a transmission

from a sero positive unit? I would say that's being done at the current time with the look-back studies.

DR. KUEHNERT: I guess I'm troubled by a lot of these statements that are being made saying that well, since we haven't seen any cases, it must not be happening, because, as you all know, we really don't have a robust surveillance system in this country to detect these sorts of infections, so it would depend on an astute clinician or laboratorian to pick it up. And it's amazing the number of serendipitous ways that we've seen it picked up in either organ transplantation or blood transfusion. And you just can't imagine how it got picked up, because it seems so coincidental, and so I really would urge caution about trying to judge the transmissibility by those data.

Now that being said, I think there's an opportunity here through the data that's already been collected, and is going to be collected in the future as far as the look-backs,

because that is really going to be critical data, because the numbers I saw today were pretty small. And I don't think I'd be able to judge anything based on those data. But I think in the future, it may say more, and it's really going to depend on the aggressiveness of the follow-up, how robust those data are, so I guess I would just encourage as much as we can that the follow-up be as complete as possible. And, of course, that's going to be dependent on the survival, in part, the survival of the recipients, which we can't do anything about, but as far as the rest of it, we should try to get as complete data as possible.

DR. NELSON: I agree with that. In fact, the study we did with David Leiby and Red Cross, it was interesting looking at cardiac surgery patients who had been transfused. We looked at the recipients, rather than the donors. And we found six cases, but neither the cardiologists, nor the cardiac surgeons, had made the diagnosis, only in one of those cases,

because they had coincident coronary disease, as well, but they also had Chagas heart disease, I think this disease has probably been grossly under-diagnosed. It's not an easy diagnosis, and I think it's been missed. But I'm impressed, this really is a pretty good test. I mean, I don't know what it's going to cost, and implementing another ELISA assay to the five or six we're doing seems feasible, to me.

DR. SIEGAL: Harvey.

DR. KLEIN: I agree with Matt. I think follow-up really is key, and there are a couple of things that I think we really need to define. We need to know about the sero negative window. We need to know if you can test someone after a transfusion three months down the line they're negative, whether it's especially if they're immuno suppressed because they haven't made antibody yet, but they may be infected, and we just don't know that. Or if we do, those data haven't been presented here, so I think we have to have that kind of information, as well as the

persistence data. We need to know something about this issue of frozen samples, because it really makes our repositories useless. If, in fact, we can't go back to the repositories and get data from that, then what are we going to do?

I've also heard that the parasite won't survive freezing, but I really haven't seen much in the way of data. This seems, to me, a very easy thing to do. I mean, how many experiments does it take, and how long to figure out whether fresh/frozen plasma can support the parasite, and that might be an important piece of information, so I think that may not stop you from either implementing, delay implementation, but I think it ought to be gotten.

DR. SCHREIBER: I agree with Matt. I think this is a condition that we need to follow closely. I don't agree with Ken here, that it's a particularly great test. With the 20 percent predictive power, positive predictive value, it's certainly twice as good as the HIV test where we're running about 9 percent in a low-risk

population. So I think one of the things that we need to do is, I like the approach of BSRI, where you're going to have a focused testing, and the possibility of that, to me, has a lot of appeal to focus down on your high-risk populations. From the numbers that Sue did and some back of the envelope calculations, I think you'd probably expect that there would be 1 or 2 percent of the people that were born in the United States, born out of the United States in Central or South America, would be infected with the agent. And I think that we do know it is transmitted by blood, so as a precautionary principle, I think we'd be remiss by not taking some action.

The other problem that I have is that we really don't have a confirmatory test. And I think that I have a lot of problem with screening tests, where you come up with a lot of people who are told that they're repeat reactive, but then you can't confirm. And I think that causes a lot of heartache on the part of people, so one of the real goals, I think, of the FDA should be to push

to have a much better confirmatory test, so that we know what we should be telling these people.

DR. Di BISCEGLIE: I would echo all of what you just said. The issue of the confirmatory test, I'm not sure that I would advise the agency to wait for the availability of a good confirmatory test. I think it clearly is needed, but the prevalence in the population that's being screened is so low, that the number of individuals affected by a false positive is fairly low; and, therefore, the impact is lesser. But, obviously, a confirmatory or supplementary test is really needed, ultimately.

DR. KLEIN: Just a couple of other points, I do think the agency needs to think prospectively about a re-entry algorithm. When a confirmatory test is available, that'll be a lot more helpful, but I think we don't have to wait for that. We assume that there is going to be something. We need to start thinking about that now.

In regards to tissues, I think in

some ways it's a little bit easier because I'm very impressed by the amount of processing that's done on a number of tissues, clearly enough to kill parasites. It seems to me all you need to do is demonstrate that your processing technique kills parasites, and then you wouldn't have to test the tissues that are treated in that way, so I would encourage industry to do that.

DR. SIEGAL: Dr. Stramer.

DR. STRAMER: Yes. I just wanted to address a couple of points. One, the look-back data, although I presented the results of screening of almost 2 million donations, and we're aggressively pursuing look-backs, and have had very good success from hospitals and getting recipients in for testing, zero out of 16 where only one is a platelet is really zero data, so I mean, we're going to need a long time to collect enough look-back data to make it significant. And even in previous studies, the numbers of platelets that have been collected from look-back studies, platelet recipients have been very, very

few, so I think we're still very early in this.

Regarding donors and parasitemia, I think another issue that was raised, we are doing PCR on all of our donors; that is, on all of our donors who participate in follow-up. Now, PCR, this is not a virus, this is a parasite, so we know these individuals may only be intermittently parasitemic, and it may take a number of follow-up samples to demonstrate that individuals are parasitemic. We have two parasitemic donors, our two youngest donors, actually, a 23 and a 27-year old who may be in the beginning of their donation lives, so we will continue to see parasitemic donors. David Leiby has published in the past doing repeated PCR on donors, that 63 percent of donors are parasitemic, so we will find those, and we will find positive look-backs. It' s just a matter of time.

And regarding supplemental testing, even in the absence of a supplemental test, as long as we have a second FDA licensed screening test, we have algorithms where you can use two

screening tests, and really increase the positive predictive value of a result to a donor.

DR. KUEHNERT: I think on the issue of the positive predictive value of the test, I mean, I think where it really causes an issue is in the situation where you have a repeat reactive, and you're trying to confirm. And that really does make a difference as far as counseling the donor, and telling them what they have. And that is a big issue, but it's going to be hard to resolve without looking at doing more studies to look at how the RIPA actually compares against other confirmatory tests. And, also, how the currently licensed test performs against tests used in other countries.

I don't fully understand what's done in Brazil. Maybe that would be helpful just for the committee to understand. They either use two or three ELISA-based tests, or some other tests. And then if one is positive, then it's considered a reactive. So I wonder, can that approach be compared against the Ortho test, as

far as comparing positive predictive values, and how that -- basically, the positive predictive value of the test. Is that being considered by the REDS II Group, the international study?

DR. BUSCH: My understanding with Brazil is, historically, they did require, mandate like two or three parallel tests, and if any of them were reactive, they deferred. And the donors who were enrolling into the RED study are the subset who are concordant reactive 10 years ago. They've moved now because their tests have improved. They've moved now to a single defined sensitive screening test, and they actually do what Sue described, they use a second EIA to serve as a confirmatory, as well as IFA.

We are anticipating bringing the positive samples from our studies into the U.S. and testing them on Ortho, and using the Ortho assay, for example, to look at change in reactivity over time, but we really hadn't thought about kind of a head-to-head comparison of Brazilian screening data with Ortho assay.

Dr. KUEHNERT: It's more the point of how good the RIPA is. And the other problem with RIPA is that it depends whose hands it's being done in. I mean, if Dr. Kirchhoff is doing it, it's as good as it can get, probably. But in other hands, it may not be, and so that is a concern. I think that is a concern, and so, again, it doesn't have an impact on blood safety per se, but it does have an impact on how the donors are counseled, and then undergo evaluation for further diagnosis and treatment.

DR. McDONOUGH: Can I ask a question? I just wanted to give a little bit of explanation on a couple of things. One is on the biology of the parasite. Even though it may not -- Sue suggested that there is an intermittent parasitemia, but it is important to know that many times there may not be parasite in the blood, to look for it by PCR or anything. It goes into the hiding, and you can also -- all the time keep stimulating the immune system, and, therefore, you will have antibody. So it doesn't

mean that if you do not find parasites in the blood, there is no parasite in the blood.

The second issue about the testing using -- supplemental testing, RIPA has its own advantages and disadvantages. However, you heard today that the other companies are also pursuing other types of tests, so I think we should keep that in mind.

DR. SZYMANSKI: Bringing up the cost of the test, and I would like to know if anybody could tell approximately how much it will cost each test, and per year in the United States? This might not be a deterrent to doing it, because I think the population in the United States is changing. And like in New England, you didn't have any of these cases at all, but there was immigration to that area, as well, and so I think it's going to be in a few years quite different, and Chagas could be much more prevalent condition everywhere.

DR. KATZ: Well, I can tell you, I can give you a range for what the test is

costing. I don't think that's illegal, is it, for me to say? It depends on who you are, but from about four and a half dollars, to somewhat over $7 dollars per test. It's not chicken feed, I would say. Under certain scenarios in my blood center it would be 5 percent of our operating budget to implement this test, under other scenarios it's much less than that, including a selective scenario that we're thinking very hard about, but a lot of that depends on what we see is the sense of this committee and the agency.

DR. SZYMANSKI: But it probably would go down within time, the price?

DR. KATZ: I'm looking into my crystal ball. I think that's the nature of this kind of activity. Eventually, I don't think it'll be $7 a test for my center forever, I hope it's not.

DR. NELSON: I'd be interested from the FDA. It sounds - there isn't a confirmatory test, but yet there is a confirmatory test, it's the RIPA. And maybe it doesn't perform perfectly

now, but what would it take to get -- I mean, as I understand it, another immunoblot, it's similar to the Western Blot that's used for HIV, for HTLV, for other confirmatory assays, so what's the status of that being approved or considered as a confirmatory test? What's the status of the science?

DR. EPSTEIN: I think the science is available. The problem is that a manufacturer or sponsor has to want to make it. And FDA has no tool to compel any manufacturer to make anything. And so it's market-driven. We've had many conversations about reference laboratories and the like, but that's not currently our system. We depend on commercialized tests.

DR. Di BISCEGLIE: Mr. Chairman, I guess just in terms of other scientific issues, we've heard a discussion between selective screening and using a blood test to screen everybody, but I've seen - I've heard almost no discussion of the science of the selective screening, the questions. I mean, we're

potentially screening a vulnerable population, vulnerable in the sense of their immigration status, their language, their socioeconomic status. And what is their willingness to answer these questions in an honest and forthright way, without the risk of coercion?

DR. DUNCAN: If I could make a suggestion, I understand that you posed that question in the context of implementation, overall, but we have a specific question related to that, and we might develop that conversation once we move to that question.

DR. STRAMER: Can I just make one more point about the RIPA, coming to the defense of the RIPA. Just because something is FDA-licensed, nothing against the FDA, it doesn't make the test any better. We've been using Western Blot for HIV since 1987, 1988. It doesn't make it a good test. The screening tests are leaps and bounds more sensitive than the Western Blot. We continue to use it. RIPA, in a sense, is a blot. I mean, you're reacting gel,

radioactive gel that's run up, separated by molecular weight against an antiserum, so it is an immunoblot of types, but it doesn't - just because, again, it's not FDA licensed, it doesn't make it any less good.

We did an evaluation of all our repeat reactives in three labs that do RIPA, and we had 100 percent concordance, so it was only a panel of 74 samples, but still, we looked at the Red Cross, David Leiby's RIPA, QUEST, and the Ortho RIPA, and they all performed identically. So I'm not sure if we could take another, even FDA licensed confirmatory, run multiple iterations, or even multiple master lots within once licensed product and get as good a concordance, so I don't really see the issue right now with RIPA.

MR. ARANA: Can I make one comment about the RIPA test? I do represent QUEST Diagnostics, and Dr. Louis Kirchhoff did train us personally in the use of the assay, did review, and was part of our validation process, and

continues to this day to review all our runs, so I just wanted to say, referring to your comment of the RIPA being in somebody else's hands. Okay.

DR. EPSTEIN: Yes. I mean, what's at issue here is assuring manufacturing consistency, and product quality. And what's being said is that absent the FDA process, we can't assure that. Now there's a parallel system in our country for lab-based testing, which is oversight under the Clinical Laboratory Improvement Act, which is a responsibility of the Center for Medicare/Medicaid Services, and not the FDA. What FDA is saying is that we're not in a position to recommend actions by regulated entities based on tests that we have not reviewed, and whose quality we cannot assure. There's also the question of what happens over time.

Now that said, I'm not asserting that there aren't very good laboratory-based tests, or that there aren't tests, nor am I contradicting

Sue. An FDA approval process validates a product claim, but it doesn't make a thing better than it is. Hopefully, however, it has honest labeling, truth in labeling. So we're missing - we're kind of mixing up issues here.

FDA is not asserting that there is no availability of laboratory-based testing for Chagas Disease, there is. And we're also not asserting that it's valueless. We're only saying that it doesn't meet the standard of the requirement to use a confirmatory test, if there is a required screen, and available supplemental test, we call it. And we're saying that we're not in a position to make recommendations for re-entry with tests whose quality we can't assure. So those are the regulatory issues, and I'm really not speaking to what may or may not be true about an unregulated test, or I should say non-FDA regulated, because there is CLIA.

DR. KATZ: I just want to say one thing, and that is, as the AABB Association Bulletin was developed and there were discussions

with the FDA about these very issues, I think that the blood community feels reasonably well served in our ability to counsel our donors who are repeat reactive, based on what's available, as Jay says, the laboratory-based testing facilities that are available.

We're good now. We finally learned the lesson on how to talk to donors about difficult serologic messes, and with what's available from QUEST and David Leiby, and Von Kirchhoff, we can tell the donors what we think is going on with reasonable precision, so it's not an insoluble thing. The positive predictive value of this assay is, in fact, superb.

DR. FINNEGAN: Can you review for me what are the good known scientific facts about Chagas in our blood system today? What do we have good data on?

DR. DUNCAN: You mean specifically in the U.S.?

DR. FINNEGAN: Yes.

DR. DUNCAN: Right. So the seven

transfusion cases, and five organ donation cases.

DR. FINNEGAN: So what percentage is that of the blood that's used? What are the percentages we're talking about here?

DR. DUNCAN: Sure. I mean, take 15 million and multiply it by 20, and that's your N, and you've got 12 on top. So that's the evidence of reported transmissions. It's not the evidence for transmissions.

DR. FINNEGAN: Okay. And any other good science that we have? Basically, you're telling me you have .000001 percent known infection rate, and we have an unquantifiable unknown infection rate.

DR. NELSON: .004 percent prevalence among donors in the Red Cross study. Is that right?

DR. FINNEGAN: But what we're worried about is preventing disease.

DR. NELSON: Well, presumably, these units weren't transfused, and I'm not sure that the transfusion medicine people would have liked

to transfuse them.

DR. KATZ: Chagas is transfusion transmitted. There is no controversy.

DR. NELSON: No question about that.

DR. KATZ: Absolutely no controversy. I think the interesting question that BSI is trying to get at, and I'm trying to get at is, do we have to screen every donor every time from now until forever, because we do, in fact, have other safety priorities that we would like to put the resources to. That's really the fundamental question. I absolutely, even in my selective strategy, I'm testing all my platelet donors when we go live, I'm going to test all of them until I have a database, because those are the people in the United States that are most strongly associated with transmission. I really think that the selective strategy probably works for whole blood donors who we take the whole blood and turn it into something else that appears less likely to transmit. I mean, that's really, certainly, my interest, and many of my

colleagues, is there a different way than we've always done things, to do this one?

DR. GLYNN: I think I agree completely with you, Lou. I think the problem right now is that there are just not enough data, so I think the screening test is, as far as I personally think, should be implemented universally to begin with, and then we need to collect data and make sure that those data are collected on all - like is it platelets on the look-backs. And then, of course, this begs for a case control study that should be done if you can identify some risk factors, that then you could think about targeted selection for your donors. But I just don't think we have enough data right now to assess selectively, you should only test these kinds of donors.

DR. SIEGAL: Okay. In the back.

DR. KLEINMAN: Yes, Steve Kleinman, Medical Advisor to AABB. Just wanted to make a comment about the selective screening, because I guess it's going to come up later, but the focus

is on asking donors specific questions, but there's another selective screening strategy, which is screen everybody once, but then if people don't leave the country, or even if they do leave the country, since you've already proven they haven't gotten - they don't have a chronic infection with Chagas, the only reason to re-screen them is to see if they've got a new incident infection. And I think that that is a potential strategy, because most people will not be exposed to new incident Chagas infection. And so you can at least think about that in the selective strategy, and it doesn't involve the validation of questions, and how people answer them, unless you want to add a travel question, and re-screen some repeat donors. So just kind of a different way to think about selective screening.

DR. DUNCAN: So we posed this question to get this kind of input, and we certainly take to heart all the comments that have been made. We're not going to ask for any

kind of vote on this question, so depending on the strength of the chair, we could either move on to the next question, or continue.

DR. SIEGAL: Or some other burning comments, why don't we move on to the next question?

DR. NELSON: It'S not a vote, it's comment. But one of the issues with regard to, I think it's biologically plausible that it's platelets that's the problem. But the other problem is that the recipients who have developed Chagas Disease were mostly immunosuppressed so they've got all kinds of things. And it seems to me that before we say that plasma that's been frozen from a Chagas Disease infected donor is now safe, it seems to me that there should be some experiments done to show that. And that's pretty obvious, that that needs to be done. It could be rigorously evaluated probably pretty easily, I think. But it may be that we just need to screen platelets, but I don't know that we have the data yet.

DR. DUNCAN: So on the second question, we wanted to focus specifically on the question of selective testing. And the question reads: "What suggestions does the committee have on the design of research studies to validate a strategy for selective screening of repeat donors?"

DR. SZYMANSKI: I agree very much with Dr. Kleinman's comments. I think it's very reasonable to do universal testing, and then test the others only - test people only once, and then only if they have visited an area where Chagas is common the second time. I think that would be very safe, and good strategy. And then you wouldn't need to test everybody all the time, which would be so expensive.

DR. DUNCAN: So a critical part of the question is, if we were to propose adopting a test everyone once, and then selectively test the returning screening negative donors, what would we need to do to show that that's an effective strategy?

DR. KLEIN: Traditionally, we've moved from selective strategies to testing. That's been the safer strategy by far, and I think before I would feel comfortable with most of the selective strategies that we've heard proposed today, I would like to have validation of the questions, and a little bit more data. We've only got a very small amount of information telling us that these selective strategies are any good, at all.

In terms of the issue of whether or not to simply screen first-time donors once, once again, I think if we get a little bit more data, and probably before there's a guidance document, we will, since so much of the country is being screened, we'll have a pretty good idea what the number of incident cases are. We'll be able to calculate that pretty well, and I think we'll have a lot better idea as to whether that's a good strategy, or whether it isn't.

DR. NELSON: It seems to me that if you were going to screen selectively only repeat

donors who traveled, you'd have to do one of two things, and that is, you'd have to ask them a different question than you ask the first-time donors about their travel, or you'd have to ask everybody about their travel to endemic areas. And it might make sense to do that, to implement a question about --

DR. KATZ: We already do.

DR. NELSON: And then after you have the data, that you could then look and see whether or not it works, because there was this one case from the early study of Chagas, where the woman denied traveling, but, in fact, had traveled, and was Chagas positive, and was found to be wrong in retrospect.

DR. KLEIN: I think we also have the data from malaria screening, as well. The cases that get through are generally people who are from endemic areas, who've gotten through the screening process, so I really do think we need to validate the questions, perhaps more so for a population that may not be native English

speakers.

DR. Di BISCEGLIE: I was going to ask somebody to tell us what travel questions are currently asked. I didn't know about malaria, but I thought we ask about travel to the United Kingdom for BSE, and excluded those donors. Is that still what we're doing now?

DR. KATZ: The question is outside the U.S. and Canada during the past three years.

DR. KUEHNERT: I guess - I mean, it seems pretty easy to say just validate the questions, but I think a lot of people around the table know that that's not a small thing, and so I guess I would encourage that if there is some sort of selective screening on that basis, that it be as simple as possible. I mean, trying to determine what are endemic areas, I'm just getting flashbacks to malaria risk, which is really, really hard. We struggle with it. We're, at CDC, trying to help, and even with a perfect map, it's very difficult, so maybe some other - I guess you just have to look at the

numbers, as far as how many you lose if you say any travel outside the U.S., or at least in the Western Hemisphere outside the U.S., as opposed to trying to pinpoint where the reduviid bugs are.

The other thing that I see as sort of a pitfall here, possibly, in looking at validation of a strategy is, if you look at repeat donors that have already tested negative, well, their positive predictive value is going to be even lower when you try to confirm that. And you're trying to run after the result to try to resolve it, and figure out whether it's a true positive. And that really is going to, I think, be very, very difficult, so that will be even more pressure to have confirmatory tests that's very, very accurate.

DR. McDONOUGH: I just want to focus here. The strategy is for you to comment on what was proposed by Brian Custer, and whether that strategy is what they propose, is it valid, or do we need to add anything more to that? I think we

need to focus on that question.

DR. KUEHNERT: And what is that - he presented some questions, so then the questions - so to validate those questions, is that -

DR. McDONOUGH: Is that appropriate, and do we need any -

DR. KUEHNERT: Well, because to validate the question - you have to validate the question, as far as whether it's really - whether the person is answering it accurately, but then, also, does it predict the test result?

DR. GLYNN: So I'm wondering if Brian can comment, are you proposing to do like a case control study, and then different scenarios afterwards in your evaluation, or if you could --

DR. CUSTER: Initially, we were not proposing a case control study, I mean, so perhaps if the committee thinks that's a good idea, we would pursue a more formal analysis. I think that we were just going to say we're asking these questions. We'll admit that these are not

necessarily the perfect questions. The question is do they correlate with testing results, and so we'll just start down that road. We don't know.

I think the other thing that I'd like to point out is that it isn't just the three questions. Perhaps, even the most relevant question is getting a handle on the country of birth in terms of some sort of testing strategy, or something along those lines, and so there are some other things. It was not just the strategies that we put forward, as the only ones we'd consider, or the only ones that are relevant.

DR. SCHREIBER: I personally don't think we should be addressing the strategy that Brian presented. I think the general issue is, is there a possibility of developing a strategy, and then how do you validate that strategy? We heard a suggestion from Dr. Kleinman, that might be a perfectly good one. Another one might be that you only screen people once a year, and if they're repeat donors, you don't screen them

again that year, so I think there are a number of variations on a theme, and I don't think it should be up to us to pick, or give a stamp of approval to something that we've heard without very much information about it. But I think what we should be able to do is say, do we think that to have a strategy like this, is a possibility, and should it be gone off and developed further, and then brought back for discussion when the study plans are firmed up?

DR. KATZ: It's important to have a clear signal to the people that make our IT systems, that this is something that we can use, because short of that, the pressure doesn't build to develop them. We do not, in general, have such systems in blood centers at this time that allow us to, with CGMP level process controls manage such systems.

DR. SIEGAL: Dr. Bianco.

DR. BIANCO: I'm Celso Bianco, America's Blood Centers. I want to go back to a point that Dr. Klein made, that is a question of

incidence. The most -- we are discussing a lot of details of strategies, but really, the most important piece of data that we need are data about the incidence of positives, that is, how many of our donors will become positive over time? And that will define what the strategy will be to select those donors for testing to prevent them from donating. If we test everybody once, like Dr. Kleinman proposed, we may be, we won't need to test them again ever, if the incidence is zero, at least in a theoretical point of view. So we need data before we discuss the strategies.

DR. FINNEGAN: I'm going to beat a dead horse. One of the things I would ask is that the American Red Cross expand their look-back across the country, because they should be able to do that, or at least to have larger areas that they look at. And I think that'll do two things. If it's geographic, it may, in fact, show you that there are areas where you only have to test once, and you probably don't ever have to

test again, and there are areas where you probably have to test every time you get a donation. But I think that kind of data is critical for you to decide what the strategy is going to be.

DR. DUNCAN: Well, Sue might want to comment, but I think their look-back is universal.

DR. STRAMER: Yes, all the look-back data I showed is nationwide. That is everything, all the repeat donors who are reactive in the study, nationwide. The regions provide us all the components that were manufactured, what happened to each and every one of those components. Those components are then traced to the hospitals. We find out if those components were destroyed, were they transfused. For every single one of those components, if they were transfused, then we trace the recipients, so we have done that for every single repeat reactive donor that we have in the study.

DR. FINNEGAN: And what's the time

frame of that?

DR. STRAMER: The time frame is we implemented testing August 28th with the clinical trial. That clinical trial for 148,969 donations went until January 27th, and then we started testing using the licensed test, and I presented the preliminary look-back numbers we have for those.

DR. FINNEGAN: So that's a year, less than a year.

DR. STRAMER: Yes, it's less than a year, and for the first four months, it was less the nationwide.

DR. FINNEGAN: So then, perhaps, a prospective study, or is there any way to look back on your previous recipients to see if anyone has gotten Chagas Disease, and then, perhaps back at the --

DR. STRAMER: When we do look-back, if there is a donor who's positive, we go back. As I said, as long as the electronic records exist, to every recipient who potentially could

have received a component from that positive donor.

DR. FINNEGAN: Right. But you may have some donors who haven't come forward, again, because they're too sick, or whatever, who may have given it previously. Is there any way to track that? Do you understand what I'm saying? Somebody who had Chagas, gave blood, that was not giving blood during the time period that you did your look-back.

DR. STRAMER: Well, we would only know if they came to donate, yes.

DR. SZYMANSKI: Do you have data on the donors who are negative, their second donation if they become positive?

DR. STRAMER: You mean along the lines of Celso's question. I have to search the database, and this is something that's in progress, to see if donors who've come back, is this their second donation, so that we can search to see how many have already had multiple donations, if we've had any sero converters. All

of our positives, so far, this is the first time they've been tested with the test. But over time, we will accumulate that information.

DR. SIEGAL: Comment in the back.

DR. LEIBY: Yes, David Leiby, the American Red Cross. I'm going to address this question, but I want to jump on the look-back question, first, because this keeps coming up, and I think it needs to be addressed head-on.

We talk about look-back, I think one of the problems we're having is that we're basing our experience of look-back on what we've seen in viral infections before. As Lou has already said, there's not a question that this parasite is transmitted by blood transfusion. That's well known, so it gets to the question of how often it happens, so we're trying to use look-back to look at that question. The problem is with viral agents, how many viruses are found in an infected unit. Millions, thank you, tons of them, yes. There's lot of viruses in an infected unit. With a *T. cruzi* unit, there may be zero, there may be

one, there may be ten, but there's very few there each time, so the risk of getting it and looking at a look-back, the look-backs are not going to be very effective at telling you how frequently it occurs. So this hang-up on look-backs is really, I think, glossing over what the real issue is here.

DR. FINNEGAN: So how do we find out what the incidence is, because as far as I can see, we do not have data on what the incidence -

DR. LEIBY: It's going to be very difficult to determine. I mean, you have a unit of blood from a blood donor. You know that they are infected by it based on antibodies, and as Hira Nakhasi says, they have the infective parasite, perhaps some cardiac tissue. It may not be in peripheral blood, so I'm giving you blood from an infected person. I'm saying go ahead, you may transfuse this to a recipient. Do we know it's infective or not? We don't know, but that's the risk you're taking, and I don't know if that's a risk you want to take.

DR. FINNEGAN: If my blood bank is in Iowa in the middle of a rural area, what's the risk?

DR. LEIBY: I will address that issue, too. Have you gone to your meat packing industry in Iowa?

DR. FINNEGAN: True.

DR. LEIBY: Lou, who works in the meat packing industry in Iowa?

DR. KATZ: If we have to administer the donor history questionnaire in Spanish, we will test in our selective screening, so yes, we have - in Iowa, for example, and one of the reasons I'm attracted to selective screening is in the census data, the number of Hispanic, Latino immigrants in Iowa is, as you may or may not guess, very, very low, but it's not zero. And there are places we do mobile blood drives, where it's high, and I want to test those donors.

DR. FINNEGAN: Okay, but my point was not well described. What I was trying to do was pick out the white born in America, hasn't left

the heartland, wouldn't know whatever kind of bug that is if he was covered with them, why are we spending money testing him?

DR. LEIBY: That's a valid question. What we're trying to do is find the individuals who are infected. Now to go to the question standpoint, question, which actually addresses the Question 2 that's up there, and Ken has alluded to one of our studies which we published in 1997 several times. When we ask questions in L.A., we asked about birth in endemic countries, we asked about time spent, six months that they had been there, and we actually looked at donors who answered no to the questions. Yes, we did a case control study, and this is published, and we found infected people among those individuals who answered no. And they were Latin American immigrants.

We also had questions - initially, we asked people if they had traveled to - very similar to what Brian proposed - if they lived in or had been in Latin America for more than six

months. We didn't ask about birth, we asked if they had been there more than six months. It turns out people who are born in Latin America, many of them didn't consider that they had spent more than six months in Latin America.

We had a similar question on the thing when we started screening those who answered yes to a question, the question was, were you born in, and lived in Latin America? They checked no. At the bottom, there is a REDS question at that time, five REDS questions, and those in REDS will be familiar with these questions. And one of the questions was country of birth, so they'd answer no at the top if they'd been born in Mexico, Central America, or South America, and in the bottom they'd write in Guatemala, or some other country, so the questions really don't work.

I think overall, the effectiveness of using questions is very difficult. And when you get into this community who we are talking about, it's a very sensitive issue, if you start asking

them where were you born? Were you born in Central America, South America, particularly with the given climate of immigration. We talked to a lot of these donors in our previous studies in L.A., tried to get them to come back in, and actually give additional samples, we found all kinds of stories that I can relate to you about what goes on in the community, what they're afraid of, and why they don't want to become involved. And so, from that standpoint, I think asking any of these questions, as harmless as they may seem, are actually very difficult, so I agree with Celso, no questions.

DR. DUNCAN: And I would just tack onto the discussion about questions, is that what's being proposed to find questions that would trigger retesting of repeat donors, and that means a person who was born in South America, tested once negative. The question is going to be, have you been outside the United States, as Matt was saying. This question could be much simpler, much more discriminating than

some question about where have you lived, or what's your ethnicity.

DR. KUEHNERT: More discriminating without being discriminating.

DR. DUNCAN: There you go.

DR. KUEHNERT: Because you're absolutely right. I mean, you take away that part of the question about foreign birth, or American citizenship, and turn it into a travel question, which is much less seemingly biased towards someone wondering why you're asking that question, for a reason other than the safety of the blood supply.

DR. DUNCAN: Right. Although, you're still going to have the problem of people answering truthfully.

DR. Di BISCEGLIE: It all comes down to the data. Does the question, whatever the question is, predict a positive test result, when that person comes back? And at this stage, we don't know, we have to gather those data, obviously. It just has to - the gold standard

has to be the test result, even although the test is not a very good standard, but that's what you have to compare the questions to.

DR. GLYNN: So I guess one other major issue is how are those data going to be collected, because I think we need those data to be able to do any of those research studies. And you can't do anything from case control, cohort study, incident studies, I think all of it should be done, but you need the data, so who and how are these data going to be collected, I guess?

DR. KLEIN: I think a lot of them are being collected right now. I mean, certainly the REDS study collecting some data. And the data from the Red Cross and Blood Services will tell you whether the travel question works, because you have a travel question on every questionnaire. I mean, you're going to get some information from just going back and looking at what we have as a screen.

DR. KUEHNERT: Right. Isn't the Uniform Donor History Questionnaire, the

abbreviated questionnaire, is there some validation process going on for that now? So there isn't any evaluation of that, because that would be very helpful, because like Harvey says, it includes travel questions that could be useful here.

DR. NELSON: It seems to me, though, if there are 15 million donors a year, or 12, or something in that range, and out of every million donors you get 60 positive, repeat positive tests, and half of - that are confirmed, and half of the donors are repeat donors, you should have some data in six months or a year that you could look at this question. It seems like - and maybe the donor questionnaire doesn't need to be changed at all, if it now - if you can tell if somebody's been to Latin America with the questionnaire as it is. I mean, it doesn't seem like it's going to be very hard to do, but it would seem to me that we need those data before we make a recommendation.

DR. McDONOUGH: I think the second

question in Brian Custer's - I think the decision process, I think the last slide that was either screen once and ask the question, or go for a couple of years, then screening everybody, and then once you can have a wash-out period so that you - data will be collected, because there will be repeat donors there, so you will find out whether there are any people coming.

DR. NELSON: Be the repeat donors that have previously been screened, that would be your numerator.

DR. GLYNN: But I think for the incidence data, at least usually, you need about two to three years of data to be able to get a number that has huge wide confidence interval.

DR. NELSON: I'm a repeat donor, interval is about every three years.

DR. DUNCAN: Yes, I think that was an important number to get on the table, that in the study that Brian Custer proposed, there would be a period of universal testing of first-time and repeat donors, and then look at how would the

question discriminate among the repeat donors. And that will take some time. It would be probably multiple years. Is that what you're thinking?

DR. GLYNN: Right. I was saying about two to three years, usually, has been the time it took to get incidence on other markers.

DR. Di BISCEGLIE: I'm a little confused. Is the study that he proposed in Brazil, or in the United States?

DR. DUNCAN: He'S talking about two studies.

DR. Di BISCEGLIE: Two studies, okay.

DR. DUNCAN: One in Brazil, one in the United States.

DR. Di BISCEGLIE: Okay. Because the incidence would be much lower here, and so the confidence interval around any number that you get for an incidence rate would be very wide, just because of the very small number of incident cases.

DR. DUNCAN: Well, you might want to

speak to it again, Brian, but my perception is the study is not primarily to identify an incidence rate.

DR. CUSTER: No, actually. And so we have, obviously, the Brazil REDS II studies, and those are very much more formal studies, and we're trying to launch similar kinds of studies. The decision analysis a separate issue, and we are not asking about incidence. I mean, to sort of go to what it is, it really is very simple at this point, and it sounds like the committee is saying they need more formal thinking, and perhaps, even a more formal analysis than just sort of correlating data. But it wasn't designed or thought to be sort of what's going to measure incidence. You would get that if you do one to two years, and it might need to be more than two years of universal testing of all donors. You will then have, incidence may not be the right word, but the actual sort of real prevalence in the donor population in the U.S.

DR. NELSON: The real issue is after

you get the incidence, does the incidence correlate completely with those who have had a travel history.

DR. GLYNN: And when you get that, you get your window period, so we need to do a lot of lab studies, as well. It should be done. And I think in REDS II, actually, you're proposing to - international, you're proposing to do several laboratory studies. Is that right, Brian?

DR. CUSTER: Yes, that's correct, actually, for sure, for Brazil, which will serve as a good model. And with the 10 years worth of follow-up we know the sero status 10 years ago, we'll do a whole battery of tests today. This does provide some important information, not only on that, but on persistent parasitemia. I mean, we don't have interval samples, but we do know 10 years later what they have, and we will be doing RIPA and PCR, and all of those tests.

DR. SIEGAL: Well, perhaps we should go on to the next question at this point.

DR. DUNCAN: Yes. So question three, "Please comment on the need for and design of studies to determine whether repeatedly reactive test results for antibodies to *T. cruzi* should be further investigated for cross-reactivity to Leishmania, plasmodium, *Paracoccidiodies Braziliensis,* or other agents when the donor lacks risk factors for *T. cruzi* infection, or a test sample is found negative by other more specific tests."

DR. Di BISCEGLIE: This just seems like a waste of time, to me. I don't see the point.

DR. NELSON: Well, these are - at least plasmodium and Leishmania are transfusion transmitted. I mean, it isn't a huge number, you're talking 100 or so.

DR. Di BISCEGLIE: Well, the test for something else.

DR. DUNCAN: The question is not whether we need to test for Leishmania for improving blood safety. It's not a blood safety

question. It's primarily a donor counseling question, and the question is, is there sufficient evidence that the test is detecting Leishmania positive, *T. cruzi* negative individuals to advise them to get Leishmania testing? Or do we need more evidence that supports that kind of consideration? We've had one suggestion from Dr. Stramer that additional information is not being gained by Leishmania testing. That's one consideration.

DR. KATZ: Yes. I mean, certainly, we were happy that Sue was going to do this, because this issue came up during the clinicals, and whatnot, and her data is getting reasonably compelling, this is not something I want my blood center to do any more, which is different than the letter I'm going to send to the physician I refer the patient to, which is to say that there are some reports that these are cross-reacting, these infections produce cross-reacting antibodies, and so, if the epidemiologic circumstances are correct, you, the clinician

that we send this person to, or the Center of Excellence, may want to think about doing that testing. But I think Sue is showing us that it's probably not really an effective use of our time and resources to be setting up these assays in blood centers as part of routine testing.

DR. KLEIN: This doesn't seem to me to be a particularly productive area, any more than when you get an STS test, if you say let's look for Lupus. It's just not very productive. You may find something sometime, but I wouldn't spend a lot of effort on doing this.

DR. KUEHNERT: I'm a little confused about the question. I mean, are we asking whether there should be more studies to determine how the donor should be counseled, about what the positive result means, are you asking should there be more studies done to see whether blood centers should have to do these other tests, because those are very different questions, because it looks like from the data we saw today, you wouldn't - it wouldn't seem reasonable to

have blood centers do these other tests. But if you're talking about the other issue, are there studies that could be done to better clarify what you tell a donor, and what you tell the referring clinician, then maybe there might be another answer. So I just wondered if you could clarify that.

DR. DUNCAN: Right, and that's an important distinction. I mean, the question could be posed, do we have enough evidence now not to recommend that blood centers do further follow-up for Leishmania?

DR. McDONOUGH: Also, you have to remember that what are the - it's not based on what the issue is - what are the risk factors which are associated, because if this is a person who has gone to Afghanistan, or Iraq, or someplace, what are - those risk factors are there, too, so I think the question is that if you are a repeat reactive, and negative on supplemental test, what do you have? And we know that this test can cross-react with Leishmania,

so is this Leishmania, does this person have Leishmania infection, and then what should that person be told about the event, so that's the key question you have to pose.

DR. Di BISCEGLIE: But I don't know why that's a blood bank question. That's a medical question. You get the letter, the donor is deferred, they go see their doctor, that's for the physician to figure out, I would think.

DR. KLEIN: What is the positive predictive value for picking up Leishmania with this test?

DR. DUNCAN: It depends on the population. In the U.S., it's probably very low. I mean, what we're - the data that we're looking at so far is 100 patients who had Leishmania, had Leishmaniasis.

DR. KLEIN: That was a rhetorical question.

DR. DUNCAN: And those are going to be potentially very low prevalence in the U.S. donor population. It's really more a question of

the performance of the test, and the characteristics of the test. Do we know enough about the characteristics of this test to recommend that medical follow-up include test for Leishmaniasis in a screening positive but follow-up testing negative individual? Or we do we need to have more studies?

DR. SCHREIBER: I, personally, don't think that we know enough, and I would recommend that we need more studies. I don't think you get to the answer by looking at a Leishmaniasis population and then look at the other test. I think when you look at a low prevalent population with the test, the numbers, to me, just were not there to come to the conclusion that there is not a problem. And while you do tell the person to go see their doctor, I think this is a population that is not big healthcare provider users, so I think it's our obligation to be able to have the best level of information, and we should be able to spend some time in answering this question. I don't think it would be a hard question to

answer.

DR. Di BISCEGLIE: I guess a broader version of what you've just said is, research is needed to understand why there are some false positives. Leishmania may be one explanation, cross-reactivity with other live species, or other situations. I think that's needed, again, for medical purposes. I don't believe for blood bank purpose.

DR. KLEINMAN: Yes, I was just going to comment from the Red Cross data that it appears that getting access to a test that's both sensitive and specific for Leishmania is a problem. I mean, I think that was one of the conclusions, so if you're going to do these studies, you have to be doing them with a test that has good both positive and negative predictive value, and it seems like these IFAs for Leishmania haven't gone through near the standardization that the RIPA for *T. cruzi* has gone through, so I think you could design a research study, but you'd need access to better

assays to do the right research study. And it certainly shouldn't be a research study that's tied to routine notification of donors, at least in my opinion.

DR. DUNCAN: That's exactly the point. And the one study that we proposed started out with well-characterized Leishmaniasis individuals that had been identified in the United States, that the CDC has access to. I agree, that one of the big problems with follow-up of ongoing donors being tested currently is that there isn't a good sensitive and specific Leishmaniasis test.

DR. SIEGAL: It sounds like we have a consensus, and maybe we should move on.

DR. KATZ: Yes. I might have read this too narrowly. I just don't want this to show up in guidance, I guess, is what I wanted to say. A requirement that we do this doesn't need to be in guidance. Those of us who are interested will certainly follow-up these donors.

DR. DUNCAN: And that's precisely why

we set this aside as a separate kind of question in the area of research needed. We would like to have feedback from the Advisory Committee about the scientific need for research, not the need for blood centers to add this to their regimen.

DR. McDONOUGH: And, also, you need to keep in mind what you heard from other test manufacturers, also, that there may not be cross-reactive, so I think it is important to keep - it's not part of what should be done, but I think it's important to remember that if you miss, what will happen in that situation.

DR. GLYNN: Well, I guess, again, I see it as a medical issue, so I think yes, the donor should be - if there is any doubt that maybe the doctor should know that they should test for Leishmania, but I don't think it has to be done within the context of blood banking.

DR. NELSON: I agree, and I think it's a clinical issue, but I think it may be incorrect that Leishmania, that very few Americans have been exposed to Leishmania. I

remember the deferral of veterans from Iraq and Afghanistan, et cetera. I think this may not be as rare as - it's not endemic, but it may not be that out of the question, that this may have occurred.

DR. SIEGAL: Okay. Next question.

DR. GREENWALD: Okay. So our question for the committee is narrow, but not necessarily easy. "Please comment on the current scientific data as it relates to the potential for transmission of Chagas Disease by HCTPs."

DR. TOMFORD: I think it's important to realize there's a big difference between blood and tissues, and that the blood is meant to be living, or at least able to stay alive. Tissues, most of the time, are meant to be dead, so given the processing that the tissues go through of freezing, we may not know whether freezing kills the parasite, but I suspect it does, given the fact it's a more complex organism than a virus. Most of these are treated by bleach, most tissues treated by bleach, and other chemicals that

really came out of the AIDS era when tissues were found to transmit AIDS. So I think it's highly unlikely that tissues would transmit this disease. There are a few fresh grafts transplanted in the United States, probably maybe 100, 200 a year, so in that population, possibly, you might say yes, there probably is some blood in those grafts. But in all other grafts the blood is taken out by chemicals, so I think it's highly unlikely that tissues would transmit Chagas Disease. Cells, perhaps, I don't know that much about cells, but most of the tissues certainly wouldn't.

DR. KUEHNERT: I guess what is challenging me a little bit is knowing about the spectrum of processing. So I would agree that most of the allografts transplanted in the U.S. are bone, and so that would be probably very little risk considering how they're processed, but then you look at fresh grafts, and there would be a very different risk. And then frozen grafts are somewhere in the middle. Then there's

corneas, which aren't processed much, at all, and so I would be - those are sort of - I think of potential concern, also, because when you look at the animal studies, I mean, the parasite goes everywhere. And so, I think there needs to be some consideration of the amount of processing involved. And then this also goes back to just the need for studies. I mean, it would be pretty simple to develop some sort of a model where you take musculoskeletal tissue that's been infected with *T. cruzi*, and freeze it for a while, and see what happens, you know, at various temperatures, but that way you could just say it, instead of trying to guess. So I guess that's what I would suggest, but I guess, the bottom line of what I'm trying to say is that there is a spectrum of processing. There is this term sterile, which also bothers me a little bit, because to most people, sterile means the lack of any organisms, but there's a healthcare standard that means a six log reduction in organisms, and depending on the organism load, that may be the same thing, or

it may not be. So I guess I would just - I would urge some careful thought about what's considered sterile, what's processed, and then what the risk is.

DR. SZYMANSKI: I would like to comment on donors who have false positive tests. And the comment is that maybe this is something temporary, and would disappear in a few months, and maybe recommendation should be to retest the donor again, and if it is then negative, that could be from some temporary infectious illness, and you don't have to worry about it. And not even to refer to any other testing, but if it persists, then further testing might be appropriate.

DR. FINNEGAN: Does the World Health Organization have some guidance on organ transplant in patients with Chagas Disease?

DR. GREENWALD: They do. We're not talking about - you want your question answered, I'm sure.

DR. FINNEGAN: Well, I think I read

something about a case -

DR. GREENWALD: In endemic countries, this is from my recollection of reading the World Health Organization report on American *Trypanosomiasis*, that the recommendations are, it's very organ-specific. Some organs they recommend in Chagas positive donors not to transplant at all, and then other ones, there's recommendations to transplant, but to treat the recipient. And, of course, they have to actually know the donor's status in order to treat the recipient.

DR. FINNEGAN: Because that was my understanding, is that other than cardiac, there pretty well was you can transplant it, but then you just need to treat the recipient for the Chagas Disease. And I would - I mean, this is sort of predictable, but I would support Dr. Tomford. I think that bone, for sure, is so well cleaned out of any other tissue, and it's been used for so long as a graft, as far as I can tell, there are no reported cases of Chagas

coming from bone grafts. And I think that the bone tendon, and the tendon units, as well, are pretty well sterilized; although, I do agree that perhaps taking some Chagas-infected tissue and putting it through the process is not a bad thing to do. But I think what's been said before, is that probably the allograft tissue is, at least for the musculosekeltal system, it's pretty safe.

DR. KLEIN: I want to emphasize that these are tissues, and not organs, and organs are totally different and they're regulated, actually, by a different part of the federal government. I want to get back to what Matt said, because I think it's very important. This is a large spectrum of things that we have here, and I bet that we could go to the literature and find that some of the processing techniques are known to kill everything known to man, if not, certainly, the Chagas organism. And right away, you could simply define things that are processed in that way you don't have to worry about it. There are other tissues, such as progenitor cells

collected by apheresis where you better test the donor, because they're going to be given fresh, and I'm absolutely sure they could transmit. Then I think there are a whole host of things in-between where we just don't have the data, but the data would be easy enough to get, where then you would be able to say if processed by this method, you don't have to worry about Chagas Disease.

DR. SCHREIBER: I think the people that are processing the different organs should easily be able to do studies to support the viability of not doing testing. I think it's not a sound ground to say that we haven't seen anything, so it doesn't exist. I think that if we don't look for it, we'll never find it, so that perhaps there might have been some cases of transmission, but we just never looked, because it is rare. But I think that just as we do in things like viral inactivation, where they're required to show how many logs removal they have, I think they should be able to do the exact same

thing in these type of tissue studies to then convince the user world that those particular studies, whether it's a tendon or a bone, in fact, are not capable, because I do have the same concern with the ocular, that we say that it's not, but perhaps you look at the eye, and maybe it's not where we should be looking. Maybe it's the left ventricular dysfunction where the Chagas shows up, and you don't look at that if you've had an ocular implant, so I think they should be able to easily show, and support the data, and come back and whatever the legal term is, or the FDA term, go for a variance, or whatever, to be exempt from some testing. And if not, I think they should be held to the same standard as the blood industry.

MS. BAKER: Following up on Dr. Kuehnert's question about freezing, I was interested in knowing if there were any studies about Chagas in sperm or semen. There was reference in the questions that we received, the issue about repeated donors to sperm banks. And

with nearly, reading in the L.A. Times one place where one gets most science, that about a million children are born in the U.S. annually through artificial insemination. I was curious about the lack of studies in the packet that we received about any transmission through sperm or semen.

DR. GREENWALD: I'm unaware of studies in sperm. And the best I could find as far as looking at congenital transmission, because it's not well studied about how it occurs, was that one study. I'm sure there's probably a few more, but showing that placental cells are infected, able to be infected by *T. cruzi*.

Dr. KUEHNERT: I just wanted to just add one more thing. We've talked about organs a little bit, and it's not the purpose of this committee, because of the way that regulatory authority runs, and the federal government, but I just want to say on the record that if there is any biologic tissue that we should be considering for screening, it should be for organ

transplantation. So maybe someone associated with that authority will read the transcripts, but I just think that's really missing from consideration. Now tissue banks work with OPOs, so that may be an opportunity to talk about that risk differential that exists.

DR. SIEGAL: Comment in the rear.

DR. LEIBY: Yes, I'd like to answer maybe some more information, offer more information to some of the questions that were posed. For semen, we've asked our reproductive council about any information they know, or they're aware of with the transmission of any parasites, I guess, via semen donation. And they couldn't find anything in their literature searches. One comment that was made, I thought was interesting, which was made at a TSAC meeting recently, as well, was that it's not been recognized as a sexually transmitted disease in endemic countries, so that might be the answer there.

For most of our donors and the grafts

I showed you, of course, were all from deceased donors, so we have no chance for retest, so we really rely on the tests to be the best they can be so we don't lose donors needlessly. That's really a huge point. For instance, just core antibody testing, total, we have a positivity rate of 4.7 percent. And for sterility, biological medical devices are 10 to the negative 3 log reduction to be labeled sterile, and that's been focused by most of our banks, but now they're going to 10 to the minus 6 log reduction for them to qualify. That's their own SAL that they set for them to meet that sterility labeling.

DR. SIEGAL: All right. Lacking any further comments, perhaps we can adjourn. Any objections? Yes, for those of you who are attending tomorrow, we will resume at 8:00 tomorrow morning.

(Whereupon, the above-entitled matter went off the record at 6:41 p.m.)