donations that are being given in the tail of an epidemic that are missed by ID-NAT that had we done four replicates, you know, we know that five percent of the donor pool in these regions got infected and yet only a very small fraction came in at exactly the time of the viremic phase.

So there is a lot of people giving in that downstream convalescent phase that a single ID-NAT is not picking them up. These units have been transfused extensively and no infections have been observed.

MEMBER KUEHNERT: The bottom line is most presumptive -- the vast majority of PVDs are confirmed. And so that's something that, you know, I think health departments, we're trying to communicate that message and --

DR. BUSCH: Right.

MEMBER KUEHNERT: -- it would be helpful for blood centers to communicate that also because that presumptive sometimes throws people.

DR. BUSCH: Right. And actually Steve Kleinman has a paper coming out soon that will really document that.

MEMBER KUEHNERT: Great.

CHAIRMAN ALLEN: Dr. Kleinman, you want to make a quick comment on that?

DR. KLEINMAN: Yes, in the 2003 data, using the ABC's presumptive viremic donation definition, which is a little different than the Red Cross, is actually 99 percent positive predictive value for presumptive viremic indicating confirmed viremic.

And I think it was kind of similar in Sue's Red Cross definition. So it's very high.

CHAIRMAN ALLEN: Thank you.

Dr. Lew?

MEMBER LEW: Just as a follow up for what was said, it sounds like the study design though, you mention this person, if you all had known he was negative at the last time, you would have told him not to come back. But he happened to come back and you all went ahead and drew blood. Is that correct? And he happened to be positive the second time?

DR. BUSCH: Correct.

MEMBER LEW: So just by the study design, you may have missed a number.

DR. BUSCH: Yes, there's no question. Again, had we done, you know, replicate NAT on further follow-up leads, on a lot of cases we would have determined that that window was longer. So it's all dependent on the sensitivity of your RNA assays just

like the HPV discussion yesterday.

CHAIRMAN ALLEN: Dr. Williams?

DR. WILLIAMS: Mike, as you are aware, the recommendation to screen donors for headache with fever symptoms within the last week was largely driven by the CDC studies of the 2002 epidemic, which found that three of the 14 implicated donors had pre-donation symptoms.

And you've speculated that IgM both would be related to symptoms and quite likely would result in a neutralized non-infective donation.

So how do you resolve those two findings?

DR. BUSCH: Well, again, you know, the symptoms, if you look at people who are presenting with symptomatic West Nile infection, with either the febrile or the neuroinvasive symptoms, you know, 100 percent of those people are seroreactive. By the time the symptoms occur, RNA screening with standard RNA assays is not sensitive enough because the primary viremia phase has been resolved.

And, you know, I think also in the natural history studies, both of the donors that you'll hear from Susan and from Blood Systems, indicate that the symptoms come on subsequent to the primary viremic phase. That symptom complex is probably immune

mediated. So these people are, you know, the neurologic symptoms are a reflection of the immune response to the infected cells.

And so to me, that that plasma viremia is neutralized isn't inconsistent at all with the fact that the symptoms are occurring concurrent with the development of the immune response.

MEMBER NELSON: Yes, but I think Dr. Williams was raising the issue that there were three cases where transmission had occurred from people who previously had symptoms. So that would suggest that maybe the virus wasn't neutralized in those three people if the symptoms were due to the West Nile infection. Isn't that what you were talking about? And I think there is a discrepancy there.

DR. BUSCH: Yes, it could be. And, again, if you -- I think we'll see from Sue, a lot of donors who aren't infected but who were caught by false positive results indicate there were symptoms in the week before. So unless you've got a controlled population, it depends on the symptom complex you're talking about.

I mean a lot of people will report after the fact that they had a headache or fever in the week or two prior to the donation. So that's not

necessarily, you know, related to their viremia that led to the transmission event.

In all of those cases, yes, the people, I think, had detectable viremia without antibodies. So that would suggest -- I mean that question of whether viremia, in the absence of any detectable immune response, can be associated with a syndrome, a fever, headache syndrome, is -- I don't think there's evidence that that does happen. But I'm sure it's controversial.

MEMBER NELSON: You know the one that leads to the really great data on -- I mean we know a lot about the biology of this virus infection because of the screening of blood donors, that's for sure.

But the one population that we can actually learn more about the length of the window and that kind of thing would be plasma donors who donate frequently. And, unfortunately, because of the viral inactivation, they're not involved.

But it would seem that if you could save some samples from an endemic area, an epidemic area from plasma donors where you'd have samples taken every few days during the epidemic, if that could be arranged, it might add to the data. It might be useful. It would require, you know, cooperation and

negotiation and what have you. But I think it might be useful.

CHAIRMAN ALLEN: Yes?

DR. KAHN: Mike, you are talking about IgM infectivity and so on, how sensitive is -- first of all, how sensitive is the IgM assay that has been used, the IgG assay? How low level of immunoglobulin detection can reach?

And second, how sensitive in the fact of discriminatory between IgG and IgM, how specific is the test for IgG/IgM? Could you please comment on that?

DR. BUSCH: Yes, I mean these aren't tests that we were involved at all in developing. There are four or five commercial assays, Focus, PanBio, Abbott had an assay. And then there's also CDC's assays. And we've done very rigorous comparative studies in there. They are virtually identical. And Kyrone also has a variety of serologic tests, both EIA and REBA format.

In terms of the time to detection of antibody, they're obviously picking up antibody, particularly IgM prior to clearance of -- you know, with significant -- I don't have data with respect to, you know, picograms of IgM or IgG.

DR. KAHN: Yes, that's exactly where I want to go because we don't know if recurrence of infection, not disease --

DR. BUSCH: Right.

DR. KAHN: -- in the presence of antibodies possibly. And one way of demonstrate that is that antibody can be treatable before outcome of diseases Dr. Klein mentioned. And as we know, IgM can last from one year to the next year.

We don't know if some is left over in the second infection from a different strain or so on because it still needs to be done if what we are detecting calling negative for IgM doesn't have any IgM at all. It's still questionable.

DR. BUSCH: Yes. And two other points, one is that these assays are IgM/IgG capture assays. And, again, all of the different assays that we evaluated had IgM and IgG configurations and they identically paralleled one another. So I think they are specific for IgM, IgG, and IgA.

The other thing we had, I think Sue will show some wonderful data on ramp-up dynamics, and we had like seven cases which had two bleeds prior to any antibody. And we thought we would get good ramp-up data. But in six of those seven cases, the viral load

actually dropped before the IgM kicked in.

So that suggested something else is underlying the control of that primary viremia besides these antibodies. Either they are complex and we can't detect free antibody because it's all bound to the virus or they are cell mediated or host, you know, replication capacity issues.

CHAIRMAN ALLEN: Okay. We are running well behind. Dr. Klein, a quick comment.

MEMBER KLEIN: Yes, just a quick comment on Dr. Williams' referral to the 2002 donors that transmitted.

While it is true that three of the 14 had symptoms prior to their donation, I think two important points need to be kept in mind. One is we weren't doing Mini-Pool NAT testing in 2002.

It may have been that those three people would have been detected by tests that are currently in place. Therefore, we don't know whether the question of headache and symptoms is necessary because we can't compare them. It would only be necessary if they were test negative. And we don't know that.

Secondly, only one of those three donors actually had the symptom of fever and headache within the prior week. The two other donors had that

symptom, I think in one case two weeks before and in one case greater than two weeks before. So our question, presumably, would not have caught those two donors anyway.

So I think this becomes important later on when we talk about the symptom question and what we should do with it. I just wanted to make those clarifications. I don't think I'm misspeaking if anybody else is familiar with the paper.

CHAIRMAN ALLEN: Okay. And that certainly is an important question.

We're going to change -- modify our schedule slightly. Dr. Stramer will speak and have the full time allotted to her to present the Red Cross data. And then we will have a break as soon as she completes her discussion. And move on to the rest of the agenda right after the break.

So, Dr. Stramer, we look forward to the Red Cross data.

DR. STRAMER: Thank you.

In order to consolidate the number of slides, I combined my title slide and my outline.

(Laughter.)

DR. STRAMER: That's about all the consolidation that you'll see. I'll present similar

types of data as Mike did with some emphasis, though, on some of the FDA questions related to the donor deferral.

I'll review our donors identified in 2003 that were positive by prospective Mini-Pool and individual donation NAT. I'll review our retrospective individual donation NAT studies.

I'll review our modeling viral dynamics. We used a little bit different approach but the time periods, as reported by Mike and me, will not be that much different although we have to sit down and really do a side by side.

Then I'll go through our 2004 data to October 19th by both Mini-Pool and individual NAT screening.

And then we've looked at some data for efficacy of donor deferral based on the headache with fever question seven days prior to donation.

Next. I've highlighted in red what I'd really like to go through to move through these slides quickly.

In 2003, we had 415 confirmed positive donors identified. We used the Gen-Probe TMA screening method as does Blood Systems. For confirmation, we repeat TMA and we do PCR, a validated

assay at National Genetics Institute, and we do IgM seroconversion in the retrieve plasma unit.

The method of IgM we used was Abbott and we have found that to be a little bit more sensitive than the CDC test and more sensitive than the Focus test in our validation.

Our overall frequency was about one in 5,700. The range of positive donors last year was from the end of June through the first day in December and 74 percent, three-quarters of our positives, came only from two states, Nebraska and Kansas, or 307 of 415.

Next. This was where we saw cases last year, again emphasizing Nebraska and Kansas.

Next. And on the previous slide, as I'll show for this year, the red dots don't indicate the number of cases, they indicate the counties. So there may be multiple cases per county. Last year we triggered -- we had developed a trigger that we used this year to initiate individual donation NAT and we did that prospectively from August 20th through the 4th of October.

Now we developed the trigger but we would have triggered earlier had we developed the trigger earlier. So we were only able to do this through the

second half of the year last year.

Through our ID-NAT studies, we confirmed 181; however only about half of those required ID-NAT for positivity. And of those ID-NAT positives, 92 percent of them, or the vast, vast majority, were IgM positive at index and only eight percent, or eight of 96, were IgM negative at index and, therefore, most likely to transmit. So that was really the yield of our ID-NAT prospective screening.

And the viral loads, in most cases, well, in all the antibody cases, were below the levels of quantitation by the NGI assay, the same issue we talked about yesterday with HB core where the NGI assays only can quant down to 100 copies per mil. So the eight that were IgM negative had viral loads between 100 and 950 copies per mil.

Next please. We then also did retrospective ID-NAT based on the request from FDA so that we could complete the entire season, at least in Nebraska, with ID-NAT screening. We did find an additional 21 NAT confirmed positive cases by ID-NAT. And all of them would have required ID-NAT for detection. None of them were detected by Mini-Pools, which is good because it corresponds with our screening data.

Of those, we had two that were IgM negative. So if you combine the eight and two for the entire season, we had ten ID-NAT positive, Mini-Pool negatives that were IgM negative. So our total positives in the two states where we were epidemic was 328. And of those, which I'll show you in a subsequent graph, 38 percent were ID-NAT detectable only with ten -- or just under ten percent being IgM negative.

Next please. Okay, this shows the entire battery of cases we detected by ID prospective, retrospective, and Mini-Pool NAT testing from our first case to our last case. What's important here is the difference between blue and all the other colors. This is the methods of confirmation.

What's blue here is those that confirmed with RNA and were IgM negative. Here you can see, as Mike showed, the ramp up of IgM positivity as the season went on. And these two lines indicate the period of time that we were doing ID-NAT testing.

Next please. Now this shows for the two epidemic states, Kansas and Nebraska, when we did see cases either that were detectable by Mini-Pool or those that required individual NAT screening for detection. So comparably to the IgM increase, these

were those donors that required both ID-NAT and were IgM positive, so increase of IgM reactivity and low level virus.

In orange here, I separated out those that were ID-NAT reactive but IgM negative, the ten I showed you. So you can see that they occurred pretty much evenly throughout the season.

Next please. Okay, using the slide Mike showed, I'm not going to dwell on the numbers but just shows you numbers that we had during each of the periods to our total of 438 positive. And, again, most of them detectable by Mini-Pool NAT.

Next please. So for the seroconversion studies and the viral dynamic studies, we used our 415 positive donors. Of those, 350 participated in follow up with 335 seroconverting.

But of those 335, we could study -- or we chose to study 186 in detail. And that was because these had multiple closely-spaced follow-up samples. And the time to the first follow up we chose for analysis was less than or equal to 35 days so that we could include the donor with the longest viremic period at their first follow-up sample.

Of the 186, 76 showed repeat TMA reactivity in multiple follow-up leads ranging from

two to 39 days. And of those 76, 12 have fluctuating or intermittent viremia.

Next please. I'll show you three examples of profiles of seroconverting donors. Blue shows you the loss of virus. This is the signal to cut off ratio on the TMA assay. The boxes down here represent the quantitative PCR at NGI. And then this is the Abbott seroconversion to IgM followed by IgG. So this donor's pretty typical in viral clearance.

Next please. Here's one where even though the virus didn't go below the cutoff of the assay, you can see kind of a decrease as IgM is coming up and then another spike before viral clearance.

Next please. And here you see one actually that went negative. We didn't have volume to do multiple reps but at least in the rep that was tested, it was non-reactive, also non-reactive by PCR. Two more reps were positive in subsequent bleeds and PCR was positive on this 19 days.

Next please. So on our modeling study, what we did is we did find three donors who we termed anchor donors. And this corresponds to what Ken had referred to in your question before about studying plasma donors where we could see closely-spaced intervals where these donors were undergoing ramp-up

viremia.

So we then were able to calculate, doing linear regression, a best fit line for the ramp up of these and then fix our other donors to this anchor line. And then calculate events based on a standardized time. So what we calculated on the three anchor donors was a .46 log increase per day or a .019 log increase per hour.

The doubling time for these three individuals, their viral infection, was just under 16 hours. And then if you back calculate, using the doubling time to one copy per mil to indicate times zero, and then use the lower limit of detection of the TMA assay of ten copies per mil, you can calculate the window period from time zero, that is one copy per mil, to NAT reactivity using the lower limit of detection of the assay.

So for ID-NAT, we calculated a window period of 2.2 days and for Mini-Pool NAT, a window period of 4.8 days.

Next please. So here you can see the anchor donors. These individuals had a range of viremia presentation between 1,400 and 3,600 copies per mil. And then between 70 hours and 92.25 hours, we actually have the times, you know, relative to

donation and their follow-up samples, had progressed to viral loads of 37,000 to 110,000. So here you can see the best fit line.

Next please. Now if you apply that best fit line and move it down to one copy per mil and apply -- you can apply the ID-NAT window period here at 2.2 days, the Mini-Pool NAT window period of 4.8 days, then if you use this line over time and look at where our IgM non-reactive donors had viral loads, this is for 241 from our 2003, it took 8.2 days to reach the median viral load of 5,800 copies per mil and 12.5 days total to reach the maximum viral load which we saw at 580,000 copies per mil.

Next please. Now for the duration of viremia study, firstly we looked at the time the donors presented from our one copy per mil to presentation. And that had a mean and median of 7.9 days and a range from 4.3 to 12.5 days.

Using the time when donors cleared virus and using an adjustment factor for donors that had a very long inter-donation interval to their first TMA non-reactive result, we calculated a range for viremia from one copy per mil to the end of detection of viremia as 6.5 to 56.4 days with a mean and median of 20.5 days.

And according to the sample size used for this analysis, it would represent 99 percent of the population.

Next please. So this graph now shows you the viral clearance in this 186 donors here giving you the 56.4-day maximum and the median and mean of 20.5 days.

Next please. Then to calculate from one copy per mil to the time of detection of IgM and IgG, we had IgM first coming up at 6.5 to 29.3 days. And a mean and median of 15.7 days. And then IgG coming up about four days later. But we had a smaller sample set for this. But the mean and median were relatively close but the IgG onset, at least the shortest onset, was about four days after IgM.

Next please. And here you can see the IgM duration from -- or the IgM detection that is starting from one copy per mil with a mean and median of 15.7 days from one copy per mil.

Next please. So if you put all of our times together, this is our timeline slide. So first I said you have an ID-NAT detection of a 2.2 point estimate. Then adding the time it takes to detect by Mini-Pool NAT, you have 4.8 days.

And then the time of donor presentation,

when donors were picked up by Mini-Pool or ID-NAT screening, we had a 7.9 day mean and median. I said it was about eight days to the median viral load detection so those two agreed.

IgM onset had a median of 15.7 days with this range. IgG onset was a little bit later. And then to show the 56.4-day maximum, here you have the viremic period only followed by IgM and IgG so I tried to combine these two colors into purple with a range of 6.5 to 56.4 days.

Next please. Okay, what happened in 2004, using the same trigger that we developed last year, we based our switch to ID on four hots NAT reactives, which is defined as a signal to cutoff ratio in the TMA assay of greater than or equal to 17 and a frequency of one in a thousand.

The actions are listed here. We did convene con calls with the regions and the labs when we saw two cases to let them know to be ready. And if regions wanted to trigger early, we gave them that option. So we then converted to ID-NAT and we stopped production of frozen transfusables.

Next please. This is where our cases occurred this year. This is only one county -- these are single counties represented, not indicating the

number of cases per county. And our hot spot, as CDC already referred to, was California although we did see a few cases in southern Arizona.

Next please. Just to highlight here where the majority of our cases occurred, we're in four counties that we screen in southern California, Los Angeles, Orange, Riverside, and San Bernadino. Where greater than one case per county was observed was also in Maricopa County but we also had a case in Pima and Cochise. We had a number of cases in Arkansas. And a number of cases in Kansas.

Next please. Overall, we saw for this year 106 presumptive positives and this is our definition based on hot cases, 99 which have confirmed which have an S/CO range of 2.8 to 37. So we will confirm positives that are not necessarily in the hot range.

During this time, we also switched to a new probe reagent from Gen-Probe which significantly decreased the number of false positive reactions we were seeing.

Next please. These are the areas we did ID-NAT. We did ID-NAT in southern California, in Arkansas, the Greater Ozarks Region, and in our Kansas region, Central Plains.

Of the 56 positives we had in southern California, 50 were detected based on ID-NAT. Even though we triggered in Greater Ozarks, we never had an ID-NAT positive. And in Kansas, we did have three of our seven that were detected by ID-NAT.

We don't know yet if these were Mini-Pool, you know, if they're ID-NAT only or Mini-Pool detectable. Those studies are still ongoing.

Next please. This is our epidemic curve of 2003 versus 2004. Certainly the 2004 data firstly are less and the curve is not as pronounced as it was in 2003.

Next please. Similarly, with confirmation we haven't seen the big upswing in IgM but we're still missing seven cases. But I don't know that that's going to change things dramatically.

Oh, on this slide, I did want to point out we used the Abbott IgM test in 2003 and then in 2004 because, unfortunately, Abbott discontinued their test, we switched to the Focus test. And based on our validation studies, we used a reduced cutoff for Focus of a .67 times the cutoff to detect reactivity.

And interestingly enough, using that reduced cutoff if you compare 2003 and 2004, we did get the same relative frequency of IgM negativity and

IgM positivity.

Next please. Okay, now I want to go into the headache with fever question. That's our Question 33 and the donor asserts on Question 33 if they answer yes. So the question is in the past week have you had fever with headache? And if it is yes, we defer the donor for 28 days and enter them into our DDR.

The above question is required from FDA, is asked from June 1st to November 30th each year, or longer as directed by the Medical Director.

However, at the Red Cross, and this I have no input in, our next software upgrade will make the question required year round. It's just not feasible for us to turn things on and turn things off. The potential for error is too great.

So as we're going through this question and the data was have, I ask you to review it carefully because it's important because we are going to be doing a question that may not have any value year round.

So to look at the efficacy of the question, we collected data from five regions, two that were West Nile prevalent in 2003, that is Nebraska and Kansas, and then three non-prevalent large regions. I chose LA, Boston, and our region in

Portland. And we had a half-million plus donations that were looked at, donors that were looked at.

So we compared the positive cases, that is detected by testing, with a yes response to fever with headache question. You would think in epidemic areas you would have more yes responses.

Next please. So the vast majority of positives, I already told you, came from two states but the vast majority of yes responses came from Boston and Oregon and they were later than when our cases, which were July and September. These positive responses to the questions started in September through November.

We only had some limited overlap in yes responses in cases in September in Nebraska and Kansas. And although the number of actual deferrals that we had was low, a yes response did not agree with West Nile cases by time or by location of the epidemic.

And if we assume all yes respondents were West Nile positive, then the sensitivity of the question -- so this is best case -- would have been 3.5 percent.

Next please. So I'm going to show you now each region very quickly. Red is where virus occurred

and blue is where a yes response occurred. So this is in Kansas. So here we had positive cases. And here we had positive responses to question. Seven versus 99.

Next. This is now Nebraska. These are our number of positive West Nile cases. And these are the number of yes responses, five.

Next please. This is southern California. We actually had two positive cases last year. They were travel related, they occurred early, and in the entire region of Los Angeles last year, we only had one donor say yes to the headache with fever question.

Next please. Now in Portland, we had one travel-related case and these were the number of yes responses in blue. So they were greater starting in July and running through November.

Next please. And lastly, Boston is my favorite. We had no cases but we had yes responses to 36 -- 36 donors answered yes. And you can see that this probably represents flu rather than West Nile.

Next please. So if you put all the data together, here are the West Nile cases and then here is the onset of a positive response to the question.

Next please. Now another way of looking at this was through our surveys of NAT-positive

donors. And Sharon Oryton will present these data at the AABB.

So all of our NAT-reactive donors -- this is from her abstract, and I'll show updated data from 2003 and 2004, but from the abstract 2003, we requested all NAT-reactive donors to complete a survey which was based on CDC's survey that we used in 2002, administered by a donor counselor. And it's completed at the first follow up prior to knowledge of confirmatory results.

So every NAT-reactive donor is given a survey so we have built in controls into the study because we have negatives and positives.

West Nile symptoms are stratified as occurring prior to, or on the day of, or after donation. Symptoms were more frequent among cases versus controls. And at least one symptom was reported by 78 percent of the cases versus 38 percent of the controls.

So we had 78 percent cases reporting symptoms which is certainly higher than one would predict for West Nile. But if you look at the numbers, we had 32 percent pre and 68 percent post. That was significantly different and of controls, an even split of when they answered yes.

Next please. So each symptom was reported by over 50 percent of the cases of donors reporting pre-donation symptoms. Fever with headache in the seven days pre-donation was not reported at the time of donation but on survey, it was reported by 4.5 percent of cases and 1.6 percent of controls.

The majority of donors' symptoms occurred post-donation. And of symptoms reported pre-donation, the fever with headache question, when asked pre-donation, did not elicit a yes response.

So we did have bias in the studies since questioning of both cases and controls did occur after a West Nile NAT-reactive notification, which is why these numbers are probably greatly elevated as far as symptoms that were reported.

If you are told you have an infection perhaps, you become creative in what symptoms I've had or you've had.

Next please. So I'll show you now four slides for control -- cases and controls for 2003 and 2004. So here we have the donors who reported at least one symptom, what the most common symptoms were that were reported. This is the updated data set. So it's 33 percent reported prior to donation. On the day of or post-donation, 67 percent.

Next please. This is what our controls reported, people who did not have West Nile confirmed. And it was an even split pre and post.

Next please. This is then the 2004 data, almost identical to what we see in 2003 where 31 percent pre and 69 percent on the day of or post.

Next please. These are the controls, again virtually a dead heat.

Next please. So in conclusion, although the number of actual deferrals to the above question was low, a yes response did not agree with West Nile cases by time or by location. And best case sensitivity for the question was 3.5 percent.

And from our survey of NAT-confirmed positive donors, we showed that the majority of donors' symptoms occurred post-donation. And if symptoms were reported pre-donation, the above question, when asked pre-donation, did not consistently elicit a yes response.

Again, there was bias in the study and so what we conclude is that the above question has no measurable value.

Thank you.

CHAIRMAN ALLEN: Thank you very much, Dr. Stramer. I've got a couple of questions.

You calculated the best case sensitivity for the question. Did you calculate a specificity for it?

DR. STRAMER: No, we had no way of --

CHAIRMAN ALLEN: Okay.

DR. STRAMER: -- well, there was no way to really do that with any type of accuracy.

CHAIRMAN ALLEN: Appreciating the problem of getting accurate symptom questions, you commented on the bias. And I'm not referring this to the question that is there but more to the laboratory results that you got.

And my question would be for donors who had asymptomatic viremia compared with those that had West Nile Fever or Meningoencephalitis, was there a different pattern in terms of the viremic data, appearance of antibody, and that sort of thing? And you probably don't have all that kind of complete information.

DR. STRAMER: No, I believe in 2003, we had five donors who actually were symptomatic. And they -- I mean who developed severe disease. And they did donate and they felt fine on the day of donation. So that's really the only information I have.

CHAIRMAN ALLEN: But in terms of the

duration of viremia or the --

DR. STRAMER: No, they were not different than the other duration of viremic individuals. We looked at that, yes.

CHAIRMAN ALLEN: Okay. Thank you.

Dr. Klein?

MEMBER KLEIN: So I think you'll find fewer headaches in Boston now that the Red Sox won the pennant?

(Laughter.)

MEMBER KLEIN: But more to the point, do you know of anyone who is doing any kind of testing of the donors who report that they have headache and fever a week before donation when they are screened and then are turned away.

DR. STRAMER: No.

MEMBER KLEIN: Is anyone testing them?

DR. STRAMER: No, we haven't done that. But in the 3.5 analysis, we just assumed everyone who answered yes was infected. And even then, it was only 3.5 percent sensitive.

CHAIRMAN ALLEN: Other questions or comments? Yes, Dr. Kuehnert?

MEMBER KUEHNERT: Just wanted to turn to the length of viremia question again. I wondered,

first of all, if you can tell us whether Red Cross has had a situation where they've had a donor test positive and then come back for their next donation and been viremic just to sort of get a reality check on whether that has occurred.

DR. STRAMER: No. I mean we're deferring the donors now who are viremic for a minimum of 28 days.

MEMBER KUEHNERT: So when they come back after 28 days --

DR. STRAMER: No, wait. Let me finish. That's one criteria. And then the other criteria is that they must test -- I mean this is what the FDA is asking, they must test ID-NAT non-reactive and have seroconverted. If we can't demonstrate seroconversion, even though they cleared virus, we yet require another sample to make sure that what we're seeing is an intermittent viremia in the absence of seroconversion.

MEMBER KUEHNERT: But if they actually --

DR. STRAMER: So it's really the time of when they would present for subsequent donation is actually far longer, in reality, than 28 days.

CHAIRMAN ALLEN: Right. If they had come in and donated a unit of blood, they were found to be

totally acceptable, donated a unit of blood, it was positive on NAT testing, because they had just donated, they would be deferred for at least 56 days, wouldn't they?

DR. STRAMER: If it's a whole blood donor.

CHAIRMAN ALLEN: Yes.

DR. STRAMER: Right. But a pheresis donor or an autologous isn't.

CHAIRMAN ALLEN: Okay.

MEMBER KUEHNERT: So you've had people come back for ID-NAT at 28 days and been positive?

DR. STRAMER: Yes, in the follow-up study.

MEMBER KUEHNERT: Right, right, in the study, okay, okay.

DR. STRAMER: Yes.

MEMBER KUEHNERT: The other question I had was just to try to compare apples to apples with Dr. Busch's data. What's the 99 percent confidence interval for length of viremia? I think --

DR. STRAMER: The outer limit was 56.4 days.

MEMBER KUEHNERT: So that was the longest that someone was --

DR. STRAMER: Well, not observed but that was calculated based on the modeling.

MEMBER KUEHNERT: Oh, okay.

DR. STRAMER: Observed was 39 days.

MEMBER KUEHNERT: So the 56.4 was a maximum 99 percent? Okay.

DR. STRAMER: Well, that was what the FDA requested, 99 percent.

MEMBER KUEHNERT: Okay. Thanks.

DR. KLEINMAN: Can I comment on that?

CHAIRMAN ALLEN: All right. Okay, Dr. Kleinman, do you want to comment on this particular point?

DR. KLEINMAN: Yes. Because, Sue, that was 56.4 days from your time zero.

DR. STRAMER: That's correct.

DR. KLEINMAN: Not 56.4 days from your time of actual detection which, if I understood your data correct, you'd have to adjust by about -- you'd have to adjust downward by about 7.9 days, I think.

So then your maximum would be 48 days from the time of detection by NAT. The model would predict a maximum viremia period of 48 days for 99 percent, right?

DR. STRAMER: Yes, Steve, you're absolutely right.

DR. KLEINMAN: Okay.

DR. STRAMER: The 56.4 days is the entire viremic period from one copy per mil to no more virus or one copy per mil on the other end. So you would have to deduct the time period from when the donor actually presented which was 7.9 days. Steve's correct.

CHAIRMAN ALLEN: Dr. Williams?

DR. WILLIAMS: We'll get a chance to discuss this more after the break. And with a number of card-carry epidemiologists around the table, it may be interesting.

But two observations. One is the observation of onsite deferral for any question be it male sex with other males or West Nile Fevers is just a shadow of the total deferral impact which largely occurs before the donors appear at the blood center. So just to keep that in mind that it's really a small proportion of the total deferral impact.

And the second comment is what we're really talking about is predictive value for the window period when the NAT assay is going to be negative for the donors. And I would maintain that you really can't get there from the data at this point.

So that, you know, as sensitivity issue

determination using, as a gold standard, the window period, donors who would not be detected by NATs, we really can't estimate at this point.

DR. STRAMER: Well, you can't -- well, you also can't estimate the value of the question.

DR. WILLIAMS: That's true.

CHAIRMAN ALLEN: Other questions for Dr. Stramer from the Committee?

All right, Dr. Busch?

DR. BUSCH: Yes, just one comment, Sue. In your follow-up symptom data on the donors, you presented that 78 percent of the cases indicated there was a symptom whereas 30 percent of the controls. And then you showed what percentage of those who reported symptoms reported the symptoms before or after.

And I just ran the numbers to calculate out. In the pre-donation symptoms, which I think is the focus of the question, you know how many prior to the index donation had symptoms, if you actually calculate out what percentage had any symptom in the cases, it's .24 percent. And in the controls, it's 14 percent.

So 24 percent versus 14 percent had any symptom. And none of them, I think, had both fever and headache before the donation whereas after the

donation, it's 53 percent in the cases and 14 percent in the controls. So the controls had identical rates of symptoms before and after.

DR. STRAMER: Right.

DR. BUSCH: And the cases really had virtually identical rates of symptoms before as did the controls where they had much higher rates subsequently. So I think it's a wonderful case control analysis that to me argues that the symptoms before are really background.

DR. STRAMER: Right. Because they're background, they blend into the controls. You are right. That's a good observation.

Okay, Sharon, the card-carrying epidemiologist.

DR. ORYTON: Having done the analysis myself --

DR. STRAMER: Well, leave it to the expert.

(Laughter.)

DR. ORYTON: -- the people that reported -- one thing that's --

CHAIRMAN ALLEN: Would you please identify yourself?

DR. ORYTON: I'm Sharon Oryton from the

FDA. One of the things that wasn't in the abstract and will be in our AABB abstract is there was a very interesting combination. So people didn't just report symptoms pre-donation or just post-donation. We had all kinds of combinations of that. And that will be spelled out.

The other thing I do want to point out is even in this population, fever with headache had a positive predictive value of 69 percent. Now granted those individuals pre-donation didn't admit to those symptoms when they donated but the symptoms themselves do have a good positive predictive value for West Nile infection.

DR. KLEINMAN: Was it after the donation or before?

DR. ORYTON: These were the ones that were pre-donation. Just looking at the 16 that did report fever with headache pre-donation, the positive predictive value was 69 percent.

CHAIRMAN ALLEN: That's 2004 data?

DR. ORYTON: That's the combined 2003/2004 data.

CHAIRMAN ALLEN: Okay.

MEMBER KUEHNERT: Could I just ask a question? Sharon, was there -- I haven't had a chance

to look at the abstract -- was there any kind of multi-varied analysis done to look at independent predictors?

DR. ORYTON: The data set really for the number of symptoms that we had really wasn't large enough to do that. And I had hoped with the 2004 data we would be able to. It didn't increase that sample size that large. And I just did that analysis really two weeks ago. So no, I haven't looked at that.

MEMBER KUEHNERT: Okay.

CHAIRMAN ALLEN: All right. We are well over our planned schedule. Any other questions or comments from the Committee?

(No response.)

CHAIRMAN ALLEN: Okay. We will take a 15-minute break here. I would like to reconvene at 11:40.

We will then go into open hearing and then Dr. Williams will make the presentations of the questions and FDA's thinking.

(Whereupon, the foregoing matter went off the record at 11:26 a.m. and went back on the record at 11:45 a.m.)

DR. SMALLWOOD: Dr. Allen.

ACTING CHAIRMAN ALLEN: We're going to move into our open public hearing. I've got three speakers who would like to speak: Dr. Jeffrey Linnen from Chiron Corporation; Dr. Steven Kleinman, combined statement from AABB, ABC, and ARC; and Dr. Brian Custer or, Mike, are you presenting his day or is Brian presenting data?

DR. CUSTER: I am.

ACTING CHAIRMAN ALLEN: Dr. Brian Custer from Blood Systems, Incorporated.

** So I need to read the open hearing announcement, and following that, we can move right into Dr. Linnen's presentation.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing sessions 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 speakers at the beginning of your written or oral statements to advise the committee of any financial relationship you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or group'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.

Dr. Linnen.

** DR. LINNEN: Okay. First slide, please.

Okay. The first thing I want to correct is I'm from Gen-Probe, not Chiron.

But this assay --

ACTING CHAIRMAN ALLEN: Sorry. I'm just reading what's on the paper.

DR. LINNEN: -- is the result of a partnership between the two companies, Gen-Probe and Chiron Blood Testing.

Okay. Next slide, please.

I want to give you an overview real quickly of the assay. This is an investigational assay, and it's currently being run on two platforms. The semi-automated version of the assay is run on the

same platform that our licensed HIV HCV assay uses, and we have recently started testing on the TIGRIS system, which is our fully automated system.

Testing on the semi-automated system started in June of 2003. Testing on TIGRIS started in August of 2004.

Next slide.

This shows the semi-automated system. I just want to comment on the throughput. This could be considered a high throughput system. If one technician is working, 182 individual donor testing results can be generated in about five to six hours. If pools of 16 donations are tested, nearly 3,000 donations, results could be obtained in the same length of time.

Next slide.

This shows the TIGRIS instrument. This is a fully automated system. It has a fully automated sample in handling and assay processing. Since I called the semi-automated system high throughput, I'll call this very high throughput. We can obtain 1,000 individual donor test results in 14 hours.

If pool testing is used, 16,000 pooled results can be obtained in 14 hours.

The other thing I want to point out is

that it has reagent dispense verification which monitors critical reagent addition steps.

Next slide.

I want to show some data comparing the performance of the two systems. This is analytical sensitivity data. It's a pretty large experiment. It uses 90 replicates at each copy level. These are the copy levels on the X axis. The bars are percent reactivity. So we're looking at 100 copies to zero copies. The lowest possible samples are at one copy, and you can see at 130 copies the performance is very similar, exactly the same. At ten copies, very similar. You can see that the semi-automated system performed slightly better in this experiment, but you can see then at the next lower copy level the results flip-flopped.

So overall I think we would conclude that the results between these two systems when compared appear comparable.

Next slide, please.

This is also a comparison of the two systems. This shows in-house specificity testing that was done at Gen-Probe. This experiment or these series of experiments along with the analytical sensitivity experiment was done with three lots. So

the results are divided among the three lots.

What we see here is about 3,000 tests for each platform and two false positives were seen in the semi-automated system. One was seen in the TIGRIS system. Eleven invalid results occurred with the semi-automated system, two with the TIGRIS system. Overall the specificity was very similar, 99.94 percent with the semi-automated system, 99.97 percent with TIGRIS.

Now, this is similar to what we have seen in the field. It's not quite as good as the specificity that Dr. Stramer showed, but we think it's representative of how the assay performs. So we think specificity is really pretty much the same on both platforms.

Next slide, please.

Okay. Now, I want to update screening for 2004. This year we have a total of 29 sites. That's compared to 24 in 2003. The first confirmed positive donation occurred in the middle of April, and this came from Florida. The confirmatory testing for 2004 is similar to what we were doing in 2003. There have been some changes. We are using a different confirmatory net assay. We're now using the Gen-Probe alternative TMA assay, which is a validated assay

that's been transferred to the Bayer Reference Testing Lab in Berkeley.

We're continuing to use Focused Technologies for IgM testing.

Next slide.

So this is an overview of the clinical results so far. Based on testing starting in June of 2003, we've tested over 15 million donations with the procleics WMB assay, and 1,100 positive donations, West Nile virus positive donations have been intercepted, and that's since the beginning of testing in 2003.

If you compare 2003 to 2004, the numbers are really quite different. Two thousand four, based on our algorithm for confirmation, we had 885 confirmed positive donations with this test, and these were primarily in Colorado and the upper Midwest.

In 2004, the numbers are substantially lower. This number is actually confirmed, positives plus probable positives, basically the same definition that Dr. Stramer used for presumptive positives, and these are primarily in the Southwest, as has been mentioned.

Next slide.

Okay. I want to say a little bit about

the testing that has occurred on the TIGRIS system. Currently, three sites are using the instrument. The American Red Cross in San Diego started in August, August 18th. Flood Systems started later in August, August 26th, and then the Bonfils Blood Center in Denver started August 30th.

Now, two additional sites are in the process of preparing the starting testing on this system. So the data that we have as of 10/6 is over 36,000 individual donor test results have been generated. We are six initially reactive results, one confirmed positive and five of the results are pending, but based on the SSTOs, most of these will be confirmed positive results.

Okay. Next slide.

I'd like to show you the confirmed and probable positives for 2004 showing the number by week on the X axis. As you can see, there's a definite peak that occurred, 8/23 or the week starting 8/16.

Next slide, please.

What's really useful is to compare it to the 2003 data, and you can see the data for 2004 almost appears like background compared to 2004, but there's a couple of interesting things when you look at this graph.

There's a peak occurs the exact same week between the two years, and there's also this phenomenon where there's a slight downturn in the number of confirmed cases and then it goes back up again. They're not exactly the same pattern, but it's very similar and we don't quite -- haven't analyzed that in detail to try to understand why that might be, whether they're coming from different geographic regions or what the case is.

Next slide.

I'd just like to recap what I've gone over. This assay has been used to identify over 1,100 West Nile virus infected donations, and again, that's since June of 2003. Testing on TIGRIS started in 2004, and based on our in-house studies with the lots that are being used for the pivotal clinical trial, we think that the two instrument platforms perform basically the same.

And one last slide. I'd like to acknowledge the NHLBI for their support in the development of this assay.

Thank you very much.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Linnen.

Any questions for Dr. Linnen, comments?

(No response.)

ACTING CHAIRMAN ALLEN: Okay. We will move on to the second presentation, Dr. Kleinman.

** DR. KLEINMAN: Good morning. I'm Dr. Steven Kleinman. I would like to announce that I do have some financial consulting arrangements with manufacturers that are involved in NAT assays.

Today I am here representing the AABB Interorganizational Task Force on West Nile Virus. That task force includes members of ABB, America's Blood Centers, American Red Cross. It also has representatives from FDA and CDC, but this statement comes from the three blood organizations that are represented on the task force.

So the Interorganizational Task Force on West Nile Virus would like to comment on the available scientific data regarding the deferral period for blood donors who had a reactive or confirmed positive screening test for West Nile Virus by NAT.

We will also comment on the recommendation that donors who are deferred based on a reactive or confirmed positive test should be tested and found nonreactive by ID NAT on a follow-up blood sample prior to their reentry.

Based on the data presented to the BPAC

today from both ARC and Blood Systems, AABB supports an extension of the deferral period from 28 to 56 days. Viremia has been found to extend for up to 39 to 49 days following a NAT positive donation, and preliminary modeling predicts that the viremic period would be less than or equal to we have 56 days here from the time of one copy per mL, but it's actually to 48 days from the time of detection for 99 percent of the West Nile virus infected donor population.

The data demonstrate that viremia beyond 28 days is at a low level and is accompanied by IgM anti-West Nile virus antibody. To date there has not been a documented case of transfusion transmission of West Nile in the presence of donor IgM.

Although the available data set supports the absence of such transmission, it is too small to provide complete assurance that transmission could not occur. Therefore, during the continuation of donor testing under IND, AABB recommends that in addition to the 56-day minimal deferral, donors who test West Nile virus NAT reactive or confirmed positive must have a non-reactive ID NAT prior to reinstatement. This ID NAT could be obtained any time after donation, could be obtained prior to the 56 days, but the donor would still be deferred for 56 days, but the donor would

still be deferred for 56 days. That's our position.

Data accumulated during the continuation of current INDs can then subsequently be reviewed and may prove to be sufficient to justify discontinuing the ID NAT testing requirement and permitting donations solely on the basis of an elapsed 56 days.

We recommend that FDA consider requiring manufacturers to include this ID NAT retesting requirement as part of their ongoing IND. Based on the modeling that predicts that the vast majority of West Nile virus NAT reactive donors will not be viremic beyond 56 days, we additionally recommend automatic reentry, that is, a procedure where no ID NAT required for those donors who do not return for an extended period of time, for example three to six months.

So what we're saying here is that if you want to reenter the donor in 56 days, you would need a negative ID NAT, but there are circumstances that if you wait long enough you wouldn't need to obtain an ID NAT and you could still reenter the donor. We think that time frame should be somewhere in the three to six month time frame.

Now, turning to the other issue in front of the committee, AABB recommends that the use of the

pre-donation question about fever and headache to interdict potential West Nile virus infected donors be eliminated. This question was added to the donor history prior to the availability of screening tests under IND presumably based -- and I think we heard today actually based -- on the data reported by Pealer, et al., for the 2002 West Nile virus season, that three of 16 West Nile virus transmitting donors reported pre-donation symptoms.

However, these symptoms were not reported in two of the donors within the seven-day period before donation. It was recognized by the CDC that this question had limited value even at the time of implementation. The data presented today by American Red Cross for 2003 do not support the efficacy of this question. The frequency of reported fever with headache did not correlate with West Nile virus incidence either by geography or by time.

Even in the unlikely event that all donors reporting fever and headache had actually been infected in the epidemic regions, the sensitivity of the question would not have exceeded 3.5 percent. Therefore, we advocate elimination of this question which has no demonstrable value and which contributes to an already complicated donor questioning process.

A further examination of the 2003 data indicates that donors who tested confirmed positive for West Nile virus had the majority of their symptoms develop post donation. Based on these data, we recommend continued encouragement for donors to report post donation information about fever with headache and for blood thinners to continue to retrieve units that are in inventory from any such donor reports.

Finally, we would like to comment on the final sentences in the agency's review of management in the appendix section of the issue summary document for this meeting. This section states that, quote, if a master pool is reactive and all individual donations are nonreactive, a fresh specimen from each of the indexed donations is tested using the original NAT and the alternate NAT method, unquote.

Under the current West Nile virus INDs, reactive pools for which resolution testing has been performed and all donations associated with the samples found nonreactive by ID NAT are released without further testing.

This is the same scheme used for licensed HIV-1 and HCV NAT assays. It is not realistic to think that an alternate sample under the strict handling requirements of the NAT assays will always be

available for testing and that results of alternate NAT on this sample would be available in time to release time sensitive components.

There are no data to support the statement that I quoted above from any of the INDs. I think that's the conclusion.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Kleinman.

Any questions or comments for Dr. Kleinman from the committee?

(No response.)

ACTING CHAIRMAN ALLEN: We will move on to the third statement. Dr. Custer.

** DR. CUSTER: Hi. I'm Brian Custer, and actually I'm an employee of Blood Systems.

What I want to do is actually talk to you about our 2003 donor survey results. We've been able to look at them in a little more detail, and they provide some insight. There are some limitations to what you can glean from the 2003 data and actual survey and the way it was implemented, but I think that it actually is informative.

So just briefly, BSI Medical Affairs staff actually administered the questionnaire. It is based on the CDC questionnaire, just slightly modified, and

then subsequently, of course, as we know, people rather than confirmed positive or not necessarily confirmed positive due to the issue with false positives, particularly during 2003.

Next slide, please.

So the people who were interviewed who ultimately then confirmed either negative or positive, 63 were negative and 141 were positive. So that's just the lay of the land, the large numbers.

The next slide, please.

Brief information on sort of who these people were demographically and also the time of the interview in relation to actually the donation, and it was fairly soon after the donation. So we don't have a lot of information on, you know, symptoms 30 days out after a donation, but in regard to age the people who confirmed positive and the people who were negative were essentially the same, and then for gender, a slight suggestion that males were more likely to be positive than females, but that's not statistically significant.

Next slide, please.

So this is a fairly busy slide. What it does is it covers all of the various symptoms that were actually inquired about during the interview or

during the survey, and you can see the first column. This column is the people who confirmed negative, and then the center column is the people who confirmed positive, and then a comparison of -- when it's on, it's on -- a comparison basically using chi square or Fisher's exact test.

And fever and headache are not the only symptoms that come out as being significantly more likely in the people who confirm positive. In fact, actually new rash was the one that was most statistically significantly more frequent in people who confirm positive, but there were other symptoms also that were more likely, such as painful eyes (phonetic) and chills and generalized weakness. So I just wanted to make that clear. It by and of itself is not going to necessarily discriminate.

Next slide please.

But to look specifically at fever, headache, and headache and fever, once again now actually the next slide I will present will actually look in relation to actually the discrimination data, but right now we're just looking at data without regard to the onset date of the symptoms. So these are people who will have donated and may have had the symptom before or may have had the symptom after.

If you do look and see that actually with regard to fever, it does seem that people who actually ultimately confirm positive were more likely to report fever than those who were negative. It's a similar situation for headache and actually also for both fever and headache, but once again without regard to the onset date.

So now moving on to the next slide, the next slide tries to break this out toward those various periods of interest, and you can see at the top actually is fever, once again, and then there's headache, and then there's headache and fever together.

If you look at fever alone, you can see that actually in the week prior to the donation, none of the people who were positive actually reported the symptoms in that interval. For headache, the distribution, once again, you can look and you can do the comparison between the negatives and the positives, but you can see that for the positives it's pretty evenly distributed when they're going to report that headache symptom.

And then finally with regard to headache and fever, once again, in that week prior to the donation actually nobody reported those symptoms

whether they were West Nile virus positive or West Nile virus negative in final confirmation in those seven days preceding the donation.

There were people who reported the symptoms prior to the seven days and also people who reported the symptoms afterwards, and that's really all I wanted to leave you with. We're just sort of looking at that data. We don't see a strong relationship between that particular seven-day interval in advance of the donation and the headache and fever combination.

Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Custer.

Any questions on these data for Dr. Custer?

One wonders whether some people consider mosquito bites to be a rash.

DR. CUSTER: That's true.

ACTING CHAIRMAN ALLEN: Yes. Dr. Williams.

DR. WILLIAMS: While the study was in place was there not a deferral question in place regarding headache with fever and a weak prior donation? So unless there were false negative

questions, you wouldn't expect to see that.

DR. CUSTER: Well, the question was in place, of course. The simple thing is that all of the people who would have been deferred for that were deferred, but now going back in a sort of retrospective questioning, then people do report these symptoms. So actually everybody reported here would not have been deferred for the symptom complex because they didn't report it at the time of donation.

ACTING CHAIRMAN ALLEN: Ken.

DR. NELSON: Why did you ask about headache and fever for more than seven days prior to donation?

DR. CUSTER: That was the design of the questionnaire, and the questionnaire asked specifically about the onset date, and so those are categorizations that were made after --

DR. NELSON: So you first asked if you had a fever, headache and --

DR. CUSTER: If you had a fever and then what was the onset date for that fever.

DR. NELSON: Because if you look at those data, there were more people reporting fever more than seven days among those who were West Nile virus positive.

DR. CUSTER: That's true.

DR. NELSON: And you know, I don't understand that.

ACTING CHAIRMAN ALLEN: I apologize, sir. Thank you very much.

We do have one additional speaker, Dr. Michael Fitzpatrick, America's Blood Centers. It was not on my list, but he does have a handout.

Dr. Fitzpatrick.

** DR. FITZPATRICK: Thank you, Dr. Allen.

I am Mike Fitzpatrick and I'm employed by America's Blood Centers as their chief policy officer.

Just a couple of slides to correlate with Dr. Stramer's information on the impact of the headache and fever question.

Next slide, please.

We surveyed our centers and got the results that you can see of 5.6 million donor interviews compared to 4.8 million West Nile virus NAT assays, meaning that about .8 million donors were deferred prior to being tested for various reasons, not just the headache and fever question, however.

The two blue lines, if you look at them, indicate a dead battery -- no. We've normalized the data as to rate per 10,000. So you're looking here at

the rate of positive tests per 10,000 samples tested for West Nile virus testing. Here you're looking at the rate of yes answers to the headache and fever question per 10,000 donors interviewed.

The blue lines, this blue line is from centers that actually had a West Nile virus positive test. So they had a donor that answered no to the headache and fever question, was subsequently tested for NAT, and the test came out positive.

This orange line indicates those centers who had yes answers to the headache and fever question, but have had zero positive West Nile NAT test results in this period, and this is July 2003 to September 2004.

And you see that the headache and fever yes answer lines track fairly well. They're getting about the same rate of positive answers regardless of other West Nile virus test are positive or whether it's in the region, and so the point of this slide is to point out that there doesn't appear to be a good correlation between the West Nile virus test results and the headache and fever question.

Next slide.

So from that we look at the -- we have similar interview deferrals. We have no correlation

to season or the geographic distribution, and we don't really see there's much value in that test. And we do have regional data. For time interest I won't show that to you, but the next slide shows actually a region that Sue talked about also.

Next, please.

And this is Nebraska. You can see here there were zero yes responses in 15,000 interviews, 14,953 tests results with 19 positive.

So even in an area where there was endemic West Nile virus and there were positive test results, there were zero yes answers to the fever and headache question.

So in regards to one other comment just to Dr. Williams on the self-deferral issue, yes, we did see a lot of self-deferrals for geographic travel when we instituted deferrals for BSE. I think it's unlikely that we're seeing a lot of self-deferrals for advertising about fever and headache and West Nile virus. The downers are asked how they feel during the interview. They're asked about their general health conditions. They're also asked an additional question about fever and headache. It's unlikely that we're seeing a lot of self-deferrals that are not being counted with the fever and headache issue.

That's all I have. Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Fitzgerald.

Questions? Yes.

DR. NELSON: Apparently if somebody answers yes to that question, they're not tested for West Nile virus or followed up, right?

DR. FITZPATRICK: Correct. If you answer yes and they're deferred, there's isn't a follow-up test, no.

DR. NELSON: There is no follow up.

DR. FITZPATRICK: Correct. They're not tested.

DR. NELSON: I mean that would be one way. You could design a study where you took a bunch of people who reported a headache and then controls and looked for West Nile virus markers then and subsequently. I mean, that might be the best way to get the answer to this question.

ACTING CHAIRMAN ALLEN: Doctor.

DR. KUEHNERT: Well, I just wanted to point out that, you know, all you're really saying is this question has poor specificity because, you know, your number of donors, you know, overwhelmed the number of West Nile virus positive individuals where,

you know, you could see the possible value of it. So, I mean, what you're really saying, they just have very bad specificity, right?

DR. NELSON: It usually occurs in December, too, right?

DR. KUEHNERT: We're not going to get into that, but yeah.

DR. FITZPATRICK: Yeah, I mean, if you look at the regional, even in the regions where as Sue showed, where you had fairly high positive test results and were considered hot regions by both CDC and the blood donor industry, there was no increase in the fever and headache yes answers.

So the raw correlation --

DR. KUEHNERT: Right, but even there the rate is, you know, one in 1,000, you know. So looking at a graph like that I don't think you could really evaluate anything except specificity.

DR. FITZPATRICK: Right. When you have very, very low prevalence, its difficult to draw a correlation.

ACTING CHAIRMAN ALLEN: Dr. Stramer, a quick comment and we need to move on.

DR. STRAMER: It's bad sensitivity and bad specificity because NAT in Nebraska, the frequency of

West Nile positives was one in 143.6 percent of those tested, and even there during the epidemic period we only saw five positives. If you take all of the positives, the yes responses, and you assume all of them are infected, as Ken, you test all of the yeses.

Let's assume all of the yeses are positive. Then the sensitivity of the question was only three and a half percent.

ACTING CHAIRMAN ALLEN: Thank you.

Dr. Lew.

DR. LEW: I think it might be worthwhile just pointing out the retrospective study that they showed where there was no positives within the time period, the one to six days, because it is retrospective, there is inherent bias in that if I had donated blood and I initially said I didn't have a fever and headache then and then now I'm asked to come back because I'm positive, I think I would try to remember. If I had a fever and headache, it was a long time ago rather than within the time period I should have deferred myself.

I mean I think it's natural for people not to want to implicate themselves.

ACTING CHAIRMAN ALLEN: Yes. Potential biases in the way in which we unfortunately need to

collect data.

Okay. Any other questions or comments?

(No response.)

ACTING CHAIRMAN ALLEN: Fine. Dr. Williams, would you present FDA's current thinking in the questions, and let's move on with our discussion?

** DR. WILLIAMS: Thanks.

Next slide, please.

I have a couple of slides before we get to the questions, hopefully to try to clarify matters rather than complicate them. So let's just hope so.

I think some key observations which you've already heard are the natural history data, specifically that the maximum observed West Nile viremic period, this point is observed at 49 days based on the information compiled to date.

The sensitivity of the current West Nile NAP testing is an underlying issue, and we saw a potential window period of six plus days before the NAP testing, mini pool NAP testing picks up infection, and as mentioned, we don't know what's going to happen in 2005. We don't know what the geographic focus will be, the timing of the epidemic or the extent of the epidemic. As it gradually moves toward the West, it could peter out as the epizootic isn't supported or,

like a hurricane, you know, it could curve back and hit somewhere else in the country as more susceptible birds are available. So there is no prediction for 2005 available at this point.

Next slide.

As mentioned earlier, data relevant to the donor screening question for West Nile symptoms is based on the CDC interview studies from the 2002 post transfusion cases that were very carefully followed up. This was published in the New England Journal in 2003, and essentially of the 14 donors implicated in transfusion cases, three of those reported prior to their donation event a constellation of symptoms, but looking at that earlier constellation, the combination of fever with headache appeared to show the most specificity for a relationship to subsequent West Nile infection.

Now, to answer the question raised earlier, of those three individuals, one reported that the symptoms occurred an interval of seven to 14 days prior to donation, indicating the difficulty in getting recall information as part of the screening process. So seven to 14 for one individual, five days prior to donation for the second individual, and 14 to 15 days prior to donation for the third.

Two arguably within the seven-day period and one clearly out of that.

Next slide.

As mentioned also earlier, the distribution of the on-site deferrals for headache and fever doesn't appear to match the patter of West Nile in terms of either time or geography. I think there are some explanations for this, which we can touch on briefly, and one observation which I don't think was mentioned here today, but some information was shared with FDA about the overall prevalence of the on-site deferral question, and at least for one American Red Cross region we were quoted a figure of approximately three per 10,000 for on-site prevalence of deferral.

Next slide.

So what I tried to do is sort of capture this issue of predictive value over the question. This is really an artificial two-by-two table to try to look at predictive value using on the top two sections of the table the three CDC interviewed donors who had symptoms, the 11 who did not, with a total of 14 implicated, and use rather than an historical control kind of a futuristic control for what the background prevalence of responses to that question, the prevalence, would be.

And I do this not so much for the numbers themselves as for the concept. The three per 10,000, the ration is what's important. If you conduct the question in a very limited area, particularly a very limited area that has a lot of West Nile epidemic focus, you can potentially reach a very high predictive value.

But as you broaden out the geographic area that the question is applied, particularly going beyond the bounds of where there is a West Nile epidemic occurring, the predictive value diminishes potentially down to nine percent if your population is 100,000, and you can imagine it gets much, much lower as predictive value if you apply this to the whole country and particularly apply this during the whole year when there is no West Nile occurring.

It's hard to have predictive value when there's nothing to predict. So it basically dilutes out the value of the question, and I think argues if there is some predictive value to the question in terms of defining window period West Nile infection, you could optimize the predictive value by applying it in a time period and a geographic area where there is a specific West Nile activity and by even potentially broadening the time frame that you're asking about

from one week to two weeks, in which case you would capture all three donors.

That has problems in and of itself in trying to screen donors for a historical event. You get into recall bias with the donors, and generally information older than a week is very tough to capture accurately, and I think that was recognized as well in defining the question.

Next slide.

This is just an extension of that model to the current situation where I agree with the statement made earlier. The only way to really get an accurate assessment of the predictive value of this question is to study the individuals who were deferred for the question, preferably in a follow-up study in the course of a West Nile epidemic. That's really the only way to determine whether or not these individuals were potential window period cases.

I think based on the definition of predictive value, you simply can't get there accurately or even approach it with the data currently available.

Next slide.

Reference is made to the study headed by Dr. Oryton, the interview study. Thirty-eight percent

of interviewed West Nile donors reported pre-donation symptoms.

I think as much as anything one of the interesting observations from that study was the median onset of symptoms which was seven to ten and a half days. Median means that half were before and half were after. So a week period for the question if the question is of any value at all is missing a large proportion of the individuals that you might want to catch.

A second observation is that 4.4 percent reported headache and fever in the week prior to donation in subsequent interview. While these are false negatives at the time of the donor screening event, I think, again, you know, stating that the donor screening process itself is inherently flawed. I think attempts have been made to improve it as much as possible by doing cognitive testing of the donor questions, but still it is certainly not a perfect process.

Next slide.

So in terms of FDA thinking from the May 2003 West Nile guidance, in the past week have you had a fever with headache is the "for example" question given in the guidance. At the time that was put

together, there were very limited data on deferral impact and crude estimates were that it might be one to three percent.

Current thinking as far as a modification of that question is if it is, in fact, retained is in the past week have you had a fever and a headache at the same time, and this is basically the reworking of the question by the donor history task force working with the National Center for Health Statistics. They arrived at a preferred wording for the question, and FDA certainly strongly supports that process.

I think one in asking a question like that needs to balance the science of what time period you're trying to capture versus recall bias with trying to question the general public on events that occurred in the past. Generally I think it is felt that going out more than three days you generally lose the value of when something happened in the past, and that's another difficulty.

Next slide.

In the May 2003 guidance, the recommendation was for deferral for evidence of West Nile infection for 28 days after symptom onset or 14 days post symptom resolution and deferral for West Nile symptoms for 28 days from the interview.

Next slide.

Current thinking there is that full West Nile infection or NAT seropositivity, the greater of the two factors, either 56 days from symptom onset or 14 days post symptom resolution, again, supported by the duration of viremia data and deferral for West Nile symptoms harmonizes with that 56 days from the time of interview.

Next slide.

With respect to reentry, FDA is considering recommendations for a negative individual donation NAT result for reentry of donors positive for West Nile NAT at the time of donation. This, of course, is a question posed to the committee and similarly following recognition of donors who had West Nile related symptoms prior to donation.

There are a couple of possibilities. One would be to similarly recommend for individual donation NAT negativity or one could potentially have an automatic reentry scheme at the normal time of reappearance of donation at 56 days and earlier reentry of that donor prior to 56 days, but after 28 days would require an ID NAT negative test result.

Next slide.

I don't know if you want to visit the

questions now, but I'll just end with one statement. That is I think the donor question was put into place based on the available data, and I think although the observations surrounding that question are interesting and certainly, you know, address the specificity of the question, the other co-factors that might be at play leading to donors reporting those symptoms, I guess I would maintain that the data to precisely address the predictive value of that question are not currently available.

Probably the best, if not the only, way to get at it would be in the context of the current donation process, to assess donors who defer based on that question, do the follow-up study and assess what their virologic status was.

Should the question be removed over time in that study, not done, the answer will never be brought to light, but certainly one wants to be conservative about the burden placed on the donor and on the blood centers and certainly use questions that have optimized predictability.

ACTING CHAIRMAN ALLEN: Before you get to the questions, Dr. Williams, why don't we let committee members ask you about any questions in terms of your presentation?

Yes, go ahead.

DR. NELSON: Is the fever and headache question asked of all donors in the U.S. or is it only asked either during West Nile virus transmission season or in geographic areas where there's proven West Nile virus?

DR. WILLIAMS: That's a very relevant question. The current recommendation is that the donors would be asked the question between the likely epidemic period of time of June 1st and November 30th and longer than that if in the opinion of the medical director there's still active West Nile activity.

Now, partly this is out of interest in capturing whenever there might be, you know, West Nile epidemic focus, foci occurring, but also I think there was a consideration that blood centers can't turn questions on and off, and to try to target it to either epizootic and epidemic activity, turn the question on, turn it off simply isn't practical. So thereby it dilutes the predictive value of the question applied over a longer time period, but I think as you saw reported for the changes made by the American Red Cross, it is simply easier to keep it in for the entire year than to turn it on, turn it off.

ACTING CHAIRMAN ALLEN: Others?

DR. NELSON: It certainly loses a lot of value if it ever had any when it's turned on or off, I guess, and the other issue is that a lot of the -- I don't know how many, but many Red Cross and other places use the CASIS system. You know, it's more difficult to put another question into that. I mean, it takes a lot more effort to do it that way. So I don't know.

DR. WILLIAMS: You know, it involves SOPs, training and as was mentioned --

DR. NELSON: Pretty cumbersome.

DR. WILLIAMS: -- there's room for error in trying to vary that process.

ACTING CHAIRMAN ALLEN: Yes, Doctor.

DR. KUEHNERT: I just had a question about the consistency of recommendations for part of the year for testing. For screening nucleic acid testing, I mean it's year round. At least that's what blood centers are doing. Now, for the question it sounds like it's variable, and I just wondered if you could sort of address that in consistency.

I'm not going to comment on the value of the question, but just sort of the concept of having --

DR. WILLIAMS: Testing is being done under

IND now, and it's, again, I think a function of the INDs themselves, as well as the operational aspects in the blood center that it's simply kept into place rather than starting and stopping, but it's being done under IND rather than as an FDA.

DR. KUEHNERT: So FDA really doesn't have any, you know, because it's under IND, any specific recommendations of when testing should take place in the year. they only have recommendations on when this question should be asked.

DR. WILLIAMS: Jay has a comment.

DR. EPSTEIN: It's correct that we do not have recommendations when testing should be done. However, in 2003, there was a lot of concern that if testing were not continued, we wouldn't get a full picture of the epidemic. There was concern particularly that mosquito activity could persist over months that are colder to the north than they are to the south, and whether there could, in fact, be transmissions ongoing in places like Florida, Louisiana, Texas.

And I think that the blood organizations have electively decided simply to continue because of the problems of starting and stopping, but there are those two issues of looking at a dynamic epidemic and

then the problem of error when you start and stop.

So it remains to be seen what will be done with continuation of testing, but it's true that there's no current FDA recommendation on that point.

ACTING CHAIRMAN ALLEN: Dr. Doppelt.

DR. DOPPELT: So I'm confused. In regards to the questions, since you can't turn the question on the form on and off if you're asking it all the time, what do you do in the northern states in the dead of winter when somebody said they had a fever and a headache? Are those patients being deferred?

DR. WILLIAMS: During the time period of recommended implementation, yes, they would be because you can't --

PARTICIPANT: You can do an MRI.

DR. WILLIAMS: -- rule out that it could be something other than a cold or flu.

ACTING CHAIRMAN ALLEN: All right. Really we are short of time. I will allow two very quick comments, Dr. Bianco and Dr. Busch, but the committee really needs the time for discussion.

Dr. Williams, please stay.

DR. BIANCO: I'll be very specific. Celso Bianco, America's Blood Centers.

The first one, Alan, is that those three

cases out of 14 and the implementation of the question that we all agreed to occurred before the introduction of testing, before NAT for West Nile became available.

The second thing is as we learned today, the window periods are very short, between two days for ID NAT up to five days for the mini pool NAT.

Third, the companies have made substantial improvements in the sensitivity of the assays that have been introduced partially this year, but that will be fully available for 2005. So my question to you is how many cases of transmission of West Nile by transfusion will be prevented if we maintain the question as it is today.

DR. WILLIAMS: i think the answer to that is currently unknown. One would have to run the study to determine its value to arrive at that answer.

DR. BIANCO: But my question --

DR. NELSON: The idea of the study obviously, we'd love to do it. Within the REDS-2 (phonetic) group we're designing some studies now that would involve attempting to get samples and test deferred donors for various deferrals, tatoos, et cetera.

There's some preliminary data from the Red Cross that's concerning in that some studies they've

been doing, same vein, only about 25 percent of donors who are deferred at history when then asked will you give us a sample and participate in the study or are willing to participate in these studies.

So the alternative of going to a finger stick or oral fluid could be potentially valuable for some serologic tests, but won't allow a NAT assay. The idea of recalling the donor subsequently and trying to reenter them if they are seropositive, you won't know whether at the time of the deferred donation they would have been viremic or seroreactive.

So although a study would be great, I just think not only the number is small, but the logistics of accomplishing it are very challenging.

DR. WILLIAMS: You were asked the question after you drew the blood? I mean do we do a --

DR. NELSON: Well, they do a hematocrit.

DR. WILLIAMS: And they do blood sticking, not a whole unit, but they take blood to qualify the donor prior to taking the unit. I would think there might be a way to do this.

DR. NELSON: Yeah, I think you'd have to consent for participation in a study separate from a donation to an IRB, you know, protocol.

DR. WILLIAMS: And having given that same

study design thought, I would add not only the overall enrollment is potentially difficult, but in studies of risk factors you also potentially get a lot of bias in who's willing to enroll. So they are very difficult designs and expensive.

ACTING CHAIRMAN ALLEN: Dr. Williams, I've got one question of you also in terms of reentry. You're proposing both for patients, donors who have been deferred for headache and fever as well as donors who had a West Nile virus NAT positive at the time of prior donation, when they come back in, you're recommending West Nile virus ID NAT negative result for reentry.

Is there a time frame on that? And the joint statement from the organizations that Dr. Kleinman read suggested that this be done as part of the IND or, in other words, that it be looked at as a question of whether it was useful, and I would like your comment on that.

DR. WILLIAMS: I think basically we're interested in getting scientific recommendations from the committee. We are not at this point, you know, introducing as current FDA thinking that after a time period one wouldn't need an ID NAT. I think particularly if data supported such a concept, it's

not unreasonable, but that's not being put forward as current thinking.

ACTING CHAIRMAN ALLEN: Other questions before we move on directly to the questions?

(No response.)

ACTING CHAIRMAN ALLEN: Dr. Williams, please read the first question.

** DR. WILLIAMS: So the first question: do the available scientific data support extending the currently recommended deferral period of 28 days to 56 days, Part A, for blood donors with a positive West Nile virus NAT screening tests, and Part B, for blood donors who report symptoms of headache with fever in the week prior to donation?

ACTING CHAIRMAN ALLEN: Okay. Let's entertain discussion of that. Go ahead and discuss either A or B together. We will vote separately on 1(a) and 1(b).

DR. NELSON: Except for a small autologous and, you know, separate donor, the interval between donation is already around 56 days, isn't it?

ACTING CHAIRMAN ALLEN: For standard whole blood donation, that's true, but for platelet aphoresis and some other procedures, it is more frequent.

DR. SCHREIBER: It seems to me that the window period data that we saw at least to me was very convincing, and there's no doubt in my mind that it's worth extending the period to the 56 days.

ACTING CHAIRMAN ALLEN: That would certainly be my feeling, and I know that Dr. Klein had to leave. His feeling was similar.

Are we ready to vote on this? Okay. Dr. Smallwood, would you call the roll for 1(a) and then we'll go ahead and do 1(b) after we do 1(a)?

DR. SMALLWOOD: Question 1(a). I'll just read this for the record very quickly. Do the available scientific data support extending the currently recommended deferral period of 28 days to 56 days, Part A, for blood donors with a positive West Nile virus NAT screening tests?

Dr. Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Kuehnert.

DR. KUEHNERT: Yes. And I'll add that, of course, I would expect data will be collected on this in the future to see if it even needs to be extended a little longer.

DR. SMALLWOOD: Dr. Quirolo.

DR. QUIROLO: Yes.

DR. SMALLWOOD: Dr. Goldsmith.

DR. GOLDSMITH: Yes.

DR. SMALLWOOD: Dr. Schreiber.

DR. SCHREIBER: Yes.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Dr. Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Dr. Allen.

ACTING CHAIRMAN ALLEN: Yes. And I would agree with Dr. Kuehnert.

DR. SMALLWOOD: There's a unanimous yes for Question 1(a).

ACTING CHAIRMAN ALLEN: Thank you. Move on to 1(b) please.

DR. SMALLWOOD: Question 1(b). I'm only reading Part B. I'll read the entire thing for correction. Do the available scientific data support extending the currently recommended deferral period of 28 days to 56 days, Part B, for blood donors who report symptoms of headache with fever in the week before donation?

Dr. Harvath.

DR. HARVATH: No.

DR. KUEHNERT: I'm sorry. I thought -- we're not going to have any discussion on this, on Part B or we already had it?

DR. NELSON: I think we should because these people haven't been proved to have West Nile virus, and if they donate, you know --

(Pause in proceedings due to power outage.)

ACTING CHAIRMAN ALLEN: I assumed that we had discussed both 1(a) and 1(b), but I agree there really wasn't any specific discussion of 1(b). We will go back and open the discussion for 1(b).

Dr. Kuehnert first.

DR. KUEHNERT: I think that, you know, the data presented really drives the point home that the test has poor specificity and, of course, the larger population that you apply it to, the lower the positive predictive value.

ACTING CHAIRMAN ALLEN: I'm sorry. When you said "the test," you mean the question?

DR. KUEHNERT: I mean the question. I'm sorry. The question.

So I don't want to say it's a bad question, but when you think about the question being

asked in December, it is a bad question. I mean, there's no issue with that.

And I'm just wondering is this vote going to be just a yes/no. Is there a way to say, you know, maybe fever with headache or fever and headache is just not what we should be looking at, that there are other symptoms that maybe are more specific, such as new onset rash.

I mean is that something that we can give input on or is it just yes or no to this question?

ACTING CHAIRMAN ALLEN: Well, yes, we can give input, but the input needs to be done as discussion rather than in response to the question. The question basically needs to be answered yes, no, or abstain, and you know, the question really is are there sufficient scientific data, and if there aren't scientific data, then the answer to the question is no.

DR. NELSON: You know, the reason for this question was to pick up donors in the window period, which is a few days, and if a donor comes back later, it makes absolutely no sense to extend this to -- we're saying the window period before PCR or antibodies is now longer than 28 days, and there's no data to support that.

So I think this is a no. This is easy to vote on.

DR. KUEHNERT: Okay. so the question is about whether the data supports extending the deferral period. In other words --

DR. NELSON: Somebody, you don't know what their West Nile virus biologic or serologic status was, but they reported fever and headache and were deferred on that basis.

So I would say that if they come back the next day, you can by then, you know, or two days later, five days later, something like that, that they're, you know, suitable to at least have screened to see if they had it.

I don't know.

ACTING CHAIRMAN ALLEN: Dr. Schreiber.

DR. SCHREIBER: I had a quick question, Alan. You gave a number of 4.4 percent. Was that 4.4 percent of the positives would be picked up with that question?

DR. NELSON: Four per thousand, wasn't it?

PARTICIPANT: No.

DR. SCHREIBER: Did I miss something?

DR. WILLIAMS: Let's see. Was that in relation to Sharon's study?

DR. ORYTON: It was 4.4 percent of donors in the survey reported fever with headache.

DR. WILLIAMS: And that's in the environment where they have already been prescreened at the time of donations. that's a false negative screening test result.

ACTING CHAIRMAN ALLEN: Dr. Epstein.

DR. EPSTEIN: Yes. I just want to respond to Dr. Nelson's point. I think as Dr. Busch made clear the concern here is the convalescent period of the infection where we know that ID NAT can pick up positive tests for viremia, and we don't know whether those units are infectious. There's no evidence that they are because all of the cases of transmission to date have had a negative antibody test.

But the concern here would be that if the donor came back and had a negative mini pool screen, you might be missing the convalescent tail if, indeed, someone who had a history of fever and headache, in fact, was infected at that time.

So the idea of the time to positive mini pool NAT is not helpful because what we're concerned about is capturing the convalescent tail of the distribution, which is where the unknown risk lies.

So I would dispute, you know, the argument

that you've made. On the other hand, I fully recognize that what we've heard today is a debate on the value of the donor screening question, and I can appreciate that it's hard to answer 1(b) without expressing an opinion on the question itself.

But I would suggest that that's part of why we have Question 3. So --

DR. NELSON: Are donors screened for antibody as well as --

DR. EPSTEIN: No, they are not.

DR. NELSON: They're not routinely screened for antibodies.

DR. EPSTEIN: No, and the reason for that consists in the data showing long-term persistence of antibody including IgM. Initially we had hopes that it could be a marker of the infection, but we now know that it can persist as long as I think 500 days in some percent of persons infected.

So if you were to use it to screen donors in regions that have had prior epidemics, you would pick up a lot of uninfected people who had an infection some time before presumably the last season.

And, again, Dr. Busch showed that I forget the exact time of follow-up, but you had a 20 percent persistence after a reasonably long period. That's of

IgM.

DR. NELSON: Right. Well, I guess we could propose screening those people for antibody. They'd have either antibody or virus, and if they didn't they'd be the majority who had a false negative or false positive screening question.

ACTING CHAIRMAN ALLEN: Dr. Goldsmith.

DR. GOLDSMITH: I guess I just wanted to add that now that there is a test that's available, these non-specific questions about fever and headache really don't serve much value and they add to the burden at the blood collection centers. And so they should be eliminated.

ACTING CHAIRMAN ALLEN: Other comments on discussion pertinent to 1(b)? Are we ready to vote?

DR. KLEINMAN: Steve Kleinman.

Just a brief comment. I think, you know, this illustrates to me that once we add a question to the donor questionnaire, you can never really provide enough evidence to show absolutely that the question has no value. I mean, it's almost impossible to get rid of something once it's added, but I think that here's an opportunity to say, you know, yes, we don't have absolute data, but our data is fairly convincing that this is not a useful question. So why would we

retain it?

ACTING CHAIRMAN ALLEN: Okay. That's not the Question 1(b) that is before us.

(Laughter.)

ACTING CHAIRMAN ALLEN: All right. Let's move ahead with voting on 1(b)

DR. SMALLWOOD: Question 1(b): do the available scientific data support extending the currently recommended deferral period of 28 days to 56 days, Question B, for blood donors who report symptoms of headache with fever in the week before donation?

Dr. Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Kuehnert.

DR. KUEHNERT: No. But that doesn't mean there might not be a better question.

(Laughter.)

DR. SMALLWOOD: Dr. Quirolo.

DR. QUIROLO: No.

DR. SMALLWOOD: Dr. Goldsmith.

DR. GOLDSMITH: No.

DR. SMALLWOOD: Dr. Schreiber.

DR. SCHREIBER: No. I would actually drop

the question.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: No.

DR. SMALLWOOD: Dr. Doppelt.

DR. DOPPELT: No.

DR. SMALLWOOD: Dr. Allen.

ACTING CHAIRMAN ALLEN: No. And I believe that Dr. Klein, I know you can't record this, but Dr. Klein would have voted in the same way from information he gave me.

DR. SMALLWOOD: The voting for Question 1(b), unanimous no.

DR. KUEHNERT: Could I jus task a point of clarification? Does that mean that the question isn't completely dropped? I mean, I think Dr. Schreiber brought this up. It's now at 28 days? The question is still asked, but at 28 days; is that right?

DR. WILLIAMS: It's currently at 28 days, and you've just recommended not to extend that to 56 days. I think in the third question where you have the opportunity to propose alternate approaches would be the place to comment on the value of the question overall.

DR. NAKHASI: Hira Nakhasi.

I think as you heard time and again, this

is a recommendation, but what we do as a policy, that will be determined later on.

ACTING CHAIRMAN ALLEN: All right. Dr. Williams, would you read Question 2 for us?

DR. WILLIAMS: Next slide, please.

Question 2. Do the scientific data support a recommendation to obtain a negative result by individual donation NAP prior to reentering --

(Pause in proceedings due to power outage.)

ACTING CHAIRMAN ALLEN: All right. I think we can go ahead with discussion. Are you able to record at this time?

THE REPORTER: Yes.

ACTING CHAIRMAN ALLEN: Okay. We will go ahead with discussion on this while we're waiting for the projector to warm up. It doesn't matter.

Dr. Lew.

DR. LEW: To try to move this along, I think there has been plenty of data to show that we are trying to look out for these low level positive patients, and so it would be important to recheck NAT prior to readmitting a person for a blood donation.

ACTING CHAIRMAN ALLEN: Other comments or questions?

Dr. Schreiber.

DR. SCHREIBER: I would agree with Dr. Lew. I would go for an individual NAT because we don't know what the window period is. We know what the point estimate is, and there might be broader distribution, and I think that I'd err on the side of caution.

ACTING CHAIRMAN ALLEN: Could I ask somebody from a blood collection organization who is familiar with lab procedures does this create a laboratory problem in terms of -- you know, I assume that if the donor otherwise qualifies what would be done would be to go ahead and draw the unit of blood and do ID.

In other words, the person would come in at 56 days, and you would then have to get a specimen of blood to do ID NAT. Tell them to come back in 48 hours and we'll give you the test results, and if it's okay -- I mean that is cumbersome.

Dr. Busch.

DR. BUSCH: I think just like the HBV reentry, I mean, FDA's position has been and certain of the procedures currently are any reinstatement sample is independent of a blood donation. So currently these donors are coming in, getting a tube

drawn essentially that's route for the serology and the ID NAT.

At least the blood organization's recommendations are at least that currently that ID NAT could be done anyplace in that 56 day or beyond period, but the donors would be deferred for at least 56 days, and you'd have to have documented a negative ID NAT at some point, not that the ID NAT be done subsequent to the 56 day deferral period.

So the donors could become eligible to give again after 56 days so long as you've documented that.

And the other point that I think is very important is about a third of the deferred donors from 2003 due to reactive NAT never did come back for that ID NAT and yet are still deferred in our systems because the current requirement doesn't give you that alternative option of waiting much longer and reversing the deferrals. That's where the AABB recommendation urged that there be a second reversal of the deferral option based on more extended time period.

ACTING CHAIRMAN ALLEN: Dr. Goldsmith, I believe you wanted to ask a question or make a comment.

DR. GOLDSMITH: I think if there is a requirement to perform the second NAT test in those who had a reactive NAT test, it would also give us a chance to learn something about the natural history of infection. So it would kind of be a built in research mechanism.

ACTING CHAIRMAN ALLEN: This is not part of the question. I think it's an important issue to discuss, however. Does anyone on the committee wish to address this suggestion as presented in the joint statement that this would be done as a period, you know, as an evaluation test during the interim period while these tests are still under IND and that a final determination would be made subsequently or would you do this on a permanent basis?

Dr. Lew.

DR. LEW: I think there is a fair amount of data shown or at least comments with the data. There are a lot of people that are intermittently positive. So I would still maintain 56 days and then rechecking because we all know with some of these tests as you get to the lower levels, it's going to be positive-negative, positive-negative. We wouldn't want to admit a patient who was negative at 26 days, but was really going on to be positive for more days.

At least that's my thought.

I think it is a built in research question.

ACTING CHAIRMAN ALLEN: Which means that it would have a finite end to it.

DR. LEW: I'd feel more comfortable negative at 56 than negative at 15 days or something.

ACTING CHAIRMAN ALLEN: Dr. Nakhasi.

DR. NAKHASI: I just wanted to focus on this question because I think those are very nice ideas, but I think that will be captured in Question No. 3 because what are the alternate ways of dealing with these criteria?

So I think if we focus on the Question 2 based on the scientific data, is it necessary to have the ID NAT at the time of entry; so I think if we focus on that, the other ideas which have been generated both from the blood organization and committee will be captured in Question No. 3.

ACTING CHAIRMAN ALLEN: All right. Why don't we go ahead as long as we're -- other comments on that?

(No response.)

ACTING CHAIRMAN ALLEN: How about on the basis of symptoms and then we'll vote separately?

(No response.)

ACTING CHAIRMAN ALLEN: I think my initial response to the symptom question is based on the answer to Question 1.

Okay. Are we ready to vote? Okay, Dr. Smallwood.

DR. SMALLWOOD: Question No. 2(a), do the scientific data support a recommendation to obtain a negative result by individual NAT prior to reentry of blood donors who are deferred (a) on the basis of a reactive NAT?

Dr. Harvath?

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson?

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Kuehnert?

DR. KUEHNERT: Yes.

DR. SMALLWOOD: Dr. Quirolo?

DR. QUIROLO: Yes.

DR. SMALLWOOD: Dr. Goldsmith?

DR. GOLDSMITH: Yes.

DR. SMALLWOOD: Dr. Schreiber?

DR. SCHREIBER: Yes.

DR. SMALLWOOD: Dr. Lew?

DR. LEW: Yes.

DR. SMALLWOOD: Dr. Doppelt?

DR. DOPPELT: Yes.

DR. SMALLWOOD: Dr. Allen?

ACTING CHAIRMAN ALLEN: Yes, with qualifications as we'll discuss under Question 3.

Dr. Lew.

DR. LEW: If I could just make one comment for B, it's that --

ACTING CHAIRMAN ALLEN: Let's finish up the voting on A and then we'll come back to B, and then you can make your comment if you want.

DR. LEW: Oh, oh, I see.

DR. SMALLWOOD: The results of voting for Question No. 2(a), unanimous yes.

ACTING CHAIRMAN ALLEN: Dr. Lew.

DR. LEW: Just a thought for the Question B. For those who are concerned that maybe the question might have some usefulness in the perfect, ideal situation, the right time, the right place, et cetera, again, this is kind of a built in possible answer in that how many people would be positive if they answered this question yes. I guess what we don't have is the control for this, the question being if you have fever and headache is it possible that you are positive, truly positive for West Nile.

Well, NAT might answer that question. I would prefer a nicely designed study, but it might be a surrogate. I don't know if it's worth the cost, but just something to think about.

ACTING CHAIRMAN ALLEN: Dr. Kuehnert and then Dr. Harvath.

DR. KUEHNERT: This might be just an omission here. It says "on the basis of symptoms." Does that mean symptoms of headache with fever as in Question 1?

ACTING CHAIRMAN ALLEN: That's how I interpreted it.

DR. KUEHNERT: Okay.

ACTING CHAIRMAN ALLEN: Dr. Harvath.

DR. HARVATH: The question I'd like to ask is the ID NAT would be performed on the reentry of blood donors who are deferred only on the basis of symptoms. So they would not have been tested previously with the mini pool NAT. Is that assumption correct?

ACTING CHAIRMAN ALLEN: That's right.

DR. HARVATH: Thank you.

DR. NELSON: Yeah, if you were going to try to figure out how many of the people had the symptoms, I think it would be better to do antibody

testing than to do an individual NAT because, you know, it would be quite variable when they would come back. The antibodies would be present in theoretically everybody except in egam globinemic (phonetic) or something like that, but an individual NAT, you know, you might have some confidence that it doesn't have virus, but you wouldn't know whether or not this person actually was infected.

ACTING CHAIRMAN ALLEN: Dr. Bianco, 15 seconds.

DR. BIANCO: Celso Bianco, America's Blood Centers.

This is a regulatory decision or recommendation that you're making. It's not the planning of a research project. This is going to be a totally biased sample, and the results are not going to contribute an answer to that question. I think Dr. Lew very clearly stated the need for appropriate controls, appropriate sampling and distribution considering the epidemic in the site where this is being done, the time of the year and all of that as a regulatory question.

ACTING CHAIRMAN ALLEN: Thank you. It is a regulatory question.

All right. Are we ready to vote? Dr.

Smallwood, Question 2(b).

DR. SMALLWOOD: Okay. Question No. 2(b), do the scientific data support a recommendation to obtain a negative result by individual NAT prior to reentry of blood donors who are deferred (b) on the basis of symptoms of headache with fever in the week before donation?

Dr. Harvath?

DR. HARVATH: No.

DR. SMALLWOOD: Dr. Nelson?

DR. NELSON: No.

DR. SMALLWOOD: Dr. Kuehnert?

DR. KUEHNERT: No.

DR. SMALLWOOD: Dr. Quirolo?

DR. QUIROLO: No.

DR. SMALLWOOD: Dr. Goldsmith?

DR. GOLDSMITH: No.

DR. SMALLWOOD: Dr. Schreiber?

DR. SCHREIBER: No.

DR. SMALLWOOD: Dr. Lew?

DR. LEW: No.

DR. SMALLWOOD: Dr. Doppelt?

DR. DOPPELT: No.

DR. SMALLWOOD: Dr. Allen?

ACTING CHAIRMAN ALLEN: No.

DR. SMALLWOOD: The results of voting for Question No. 2(b), a unanimous no.

ACTING CHAIRMAN ALLEN: Next slide, please.

Question 3, are there other alternatives that FDA should consider regarding criteria to reenter donors who are deferred for West Nile based on either NAT or symptoms -- and I think this one as well means headache with fever -- in the week prior to donation?

I think it's fair to add that in addition to reentry which is specified in the question that we would certainly welcome discussion regarding other aspects of the screening process.

ACTING CHAIRMAN ALLEN: This question is open for discussion. There is no voting here. This is discussion only. So directed comments are welcome in addition to what's already been said.

Dr. Quirolo.

DR. QUIROLO: Well, I think it's the wrong question. So I think the question should be fever with a new rash within the week if you're going to ask any question at all, and also even though it's not practical probably for the blood centers, I think it shouldn't be asked year around. It should be asked only during a time when there was an epidemic or there