1 because the budget doesn't allow testing for
2 as much neutrophil antibody as we would like
3 to do.
4 And so the original plan was
5 really based on two issues, to only screen a
6 portion of the subjects for neutrophil
7 antibody, was based on the fact that it's a
8 fairly low throughout assay, so logistics,
9 but it would just take more time, and then it
10 was based on cost, and I think that we have
11 also evolved to the idea that neutrophil
12 antibody testing is probably more important
13 than we might have thought originally.
14 The original plan, when we--the
15 way we solved this problem in the original
16 planning, when we realized we couldn't afford
17 it, was we said we would put down this
18 repository, and then as techniques got
19 better, you know, we might not be able to do
20 this in the same timeframe as HLA. We could
21 access the repository. So I agree with you.
22 I think it would be helpful if we could

1 screen the whole repository.
2 The reason we decided to start
3 with the HLA antibody positives is based on
4 the supposition that women who form, or men
5 who form HLA antibodies would be better
6 immune reactors and we might see a higher
7 neutrophil antibody rate in those people
8 versus people without HLA antibodies.
9 I think there's some data to show
10 that's true but I don't think it's really
11 that solid. And then if we found a very low
12 rate of neutrophil antibodies in people with
13 HLA, well, based on that rate we could decide
14 what our yield would be from the non-HLA
15 positives and then decide if it was worth it.
16 But I totally agree, I actually
17 agree, that I think if we could screen more
18 people for HNA, that would be a big
19 contribution.
20 DR. SIEGAL: Okay. Thank you very
21 much. Dr. Bianco will speak next,
22 representing the America's Blood Centers

1 experience with TRALI.
2 DR. BIANCO: Thank you very much
3 for the opportunity to be part of this
4 discussion.
5 I want to raise a few points with
6 limited amount of data, but try to add some
7 perspectives to the discussion that we are
8 having today. First is I think that we
9 should think a little bit about what
10 triggered this meeting, these discussions,
11 and all that, and essentially all of us are
12 trying to comply with an ABB set of bulletins
13 and standards that have asked that we address
14 the issue of TRALI, and obviously based on
15 fatality data from FDA, but--and other data
16 that I'm going to discuss a little bit.
17 But even if these are not really
18 standards from the ABB and there is no
19 regulatory mandate, there is a consensus, I
20 think, among all of us in transfusion
21 medicine, that we should be doing something
22 about it.

1 The other important thing was the
2 experience in the United Kingdom, and we
3 didn't talk much about it, but since the end
4 of 2003, based on data that they obtained in
5 their Serious Hazards Of Transfusion, or
6 SHOT, there is a hemovigilance system that
7 was created in England and spread to the U.K.
8 and all of Europe, today, and the system is a
9 voluntary system that has about ten years of
10 experience at this point.
11 They decided to use mostly male
12 plasma for transfusion in recipients, in an
13 attempt to reduce the incidence of TRALI.
14 But they have special issues regarding
15 plasma, that are very different from ours.
16 First of all, they don't use their plasma for
17 fractionation. They only use plasma for
18 transfusion and not for all the transfused
19 patients.
20 For instance, people, patients
21 that are 16 years old, or younger, will
22 receive plasma that has been imported from

1 the United States and actually has been
2 treated by methylene blue, and because of
3 their concern with variant CDJ.
4 These slides were loaned to me,
5 nicely, by the National Blood Service, and I
6 just wanted to emphasize a couple of things
7 from the SHOT data. First of all, we are
8 making an effort to move to mostly male
9 plasma, or predominantly male plasma, as
10 written in the briefing document. But if we
11 look at what the Brits have done after
12 essentially three years of experience, is
13 that they have kept in the yellow line, more
14 or less their distribution of plasma at 90
15 percent, because even with all the effort and
16 the experience, they have not been able to
17 maintain the supply of AB plasma, if they
18 don't work at the 90 percent.
19 They had a substantial reduction
20 in TRALI that has been attributed to plasma.
21 They have a slightly different definition
22 than we have in terms of TRALI. We, based on

1 the Canadian's consensus conference, and then
2 in HLBI, we used the six hour timeframe, and
3 when they started all these SHOT studies,
4 they have defined TRALI as pulmonary acute
5 lung injury happening within 24 hours of
6 transfusion.
7 This may have lessened the
8 specificity of the definition but according
9 to what they say in many of the discussions
10 we had, I think that the vast majority of the
11 cases are within the six hours.
12 And they had, in the last several
13 years, a substantial reduction, from 20
14 highly- likely cases in 2003, to 10, and to
15 three cases in 2005.
16 If you look at the cases, of
17 reported cases of TRALI and the deaths
18 associated with TRALI, again, that over this
19 ten years experience, or nine years
20 experience, there has been a substantial
21 decline in deaths, and while the number of
22 cases reported continues to be about the

1 same, but here, those cases are all combined.
2 The highly likely, the probably, and the
3 suspected cases.
4 So these drove a lot of our
5 thinking today in terms of one intervention
6 that could be used to reduce the incidence of
7 TRALI. Their results were very encouraging.
8 They had fewer reports of TRALI following
9 FFP and platelet transfusions, fewer total
10 reports of suspected TRALI, and fewer deaths.
11 However, there are many issues
12 that we should be aware, as we analyze, as we
13 interpret these data. First of all, it's a
14 passive reporting system. There are no
15 denominators in the SHOT data. Second, they
16 have focused their definitions, they have
17 done antibody studies and the "highly likely"
18 cases that they call are cases where they
19 identify an antibody through HLA antigens.
20 And mostly to HLA, not to much to
21 neutrophil antigens.
22 The other bullet is that there has

1 been a substantial decline with a lot of
2 education and a big effort placed by the
3 National Blood Service, to rationalize
4 utilization, and there has been a reduction
5 of about 15 percent in the use of blood
6 products in the last five years. The 15
7 percent was measured in terms of red cells
8 but there was a reduction of plasma. I'm not
9 sure about the amount in the reduction in
10 plasma.
11 A substantial number of cases
12 continue to be reported, and also, with all
13 the discussion about TRALI, the clinician
14 awareness has increased, the diagnosis is
15 made earlier and the interventions in terms
16 of approaching the patient have been better
17 in recent times.
18 Obviously, we had a very healthy
19 discussion, and particularly because of the
20 data, or the studies that Steve just
21 presented to us, but we still have a lot of
22 unresolved questions in terms of antibodies

1 that we would like to raise. The actual
2 proportion of TRALI reactions.
3 It appears from the data presented
4 by Dr. Benjamin, that about 60 percent of the
5 reactions that he was reporting, were
6 associated with males and antibodies, but we
7 don't know exactly what is this proportion.
8 We are still discussing assays, cutoff, and
9 more importantly, if we go to some screening
10 program, what antibodies and what amounts of
11 antibodies have clinical significance?
12 If we are talking about 25 percent
13 of multiparous women having antibodies to
14 HLA, we didn't see that high number of TRALI
15 reactions that could be attributed to that,
16 and actually, there are some studies, in more
17 recent times, and I did the references there,
18 that showed that a lot of the TRALI, a lot of
19 it, the products with antibodies to HLA, when
20 transfused, will not necessarily induce TRALI
21 even when there is a cognate antigen in the
22 HLA system.

1 We talked a little bit about the
2 biologic response modifiers, but, again, yes,
3 there may be a combination of both events,
4 the antibody and the biologic response
5 modifier, but we don't know what is the
6 proportion, really, in which the biologic
7 response modifier plays a role versus the
8 HLA.
9 With the approaches, the
10 interventions like the male plasma, we are
11 looking more at the HLA antibody and
12 neutrophil antibody than to the biological
13 response modifier.
14 We also talked a little bit about
15 donor-related questions and issues. The
16 questioning about pregnancies, miscarriages,
17 abortions, and the importance that each one
18 of these events have in triggering the
19 antibody response, how we would question
20 donors, how we would approach these as
21 subsequent donations. We have issues of
22 donor notification that also were raised very

1 appropriately.
2 We all know that if we defer a
3 donor, for instance, for being implicated in
4 cases of TRALI, something like that, that the
5 donor must be notified.
6 But do we need to notify donors if
7 we, for instance, start using mostly male
8 plasma? Do we have to tell people? Do we
9 need to tell donors that we need the antibody
10 testing for HLA, when there is no
11 significance to their health?
12 And do we have to notify an
13 antibody-positive donor if we are not
14 deferring a donor?
15 There are many issues that would
16 affect timeline for implementation. Dr.
17 Benjamin discussed them, in detail, so I'll
18 go very quickly, that is, in a short period
19 of time, interventions like moistly male
20 plasma increase proportion of the plasma, 24
21 hour frozen plasma, and platelets from whole
22 blood, pooled platelets, probably can be

1 implemented.
2 Changes in donor mix, in terms of
3 proportion of male versus female donors, for
4 instance, in apheresis, and other procedures,
5 will be a much more difficult role to
6 achieve.
7 Knowing that I was going to be
8 here, I asked ABC members through a survey, a
9 little bit about their plans on how they
10 intended to response to the ABB bulletins.
11 And here, I asked what were they
12 considering in terms of moving female plasma
13 to recovered plasma, and moving to 24-hour
14 plasma. And I saw that probably by the end
15 of this year, 90 percent of the members of
16 ABC plan to have predominantly male plasma
17 implemented at different times, and about
18 half of them were planning to increase,
19 substantially, the proportion of 24-hour
20 plasma versus FFP.
21 I think that there is still a
22 concern that the customers, the hospitals,

1 may not receive the--since most of the plasma
2 that has been distributed by ABC members is
3 fresh frozen plasma, there is still some
4 concern that hospitals and physicians may not
5 accept it without a good, extensive
6 educational program.
7 What their members in smaller
8 numbers are considering, and because of the
9 many issues that we discussed here, is the
10 use of antibodies to, either in a selective
11 mode, or for certain populations, to detect
12 antibodies to HLA, or to ask specific
13 questions of donors, because of more
14 difficult issues that they will have to do.
15 This will happen more slowly and
16 there is a lot of concern about the
17 technologies available, automation, and even
18 issues of cutoff that were well-discussed a
19 few minutes ago.
20 And finally, in terms of how to
21 deal with the changes in platelets, many of
22 the centers plan to supplement some of the

1 apheresis platelets with whole blood
2 platelets, but again, there is more of a
3 tendency of looking to some intervention with
4 the apheresis platelet donor, that would
5 allow many of them to continue donating, if
6 they are shown to be safer donors.
7 And this is consideration for
8 antibodies and deferrals. Members are
9 considering mostly to look for an antibody
10 assay that would be feasible, and that would
11 allow the selection of the apheresis donors.
12 I'm coming to the end and I wanted
13 to express some of the concerns of the
14 members. When TRALI became a part of the
15 agenda of BPAC, obviously they all woke up
16 and were concerned about what they thought
17 that would be premature regulatory actions
18 that may remove flexibility in TRALI risk
19 reduction measures. Strict approaches. We
20 know that they will not eliminate TRALI and
21 will affect product availability.
22 Suppose that we had a decision

1 that we should only use male plasma, for
2 instance, and certainly that's not the tone
3 of the discussion here today. The other
4 thing that concerns a lot our members, and
5 ourselves, is that we are creating somewhat
6 unrealistic expectations, with all the talk
7 and all the effort that we are applying to
8 TRALI, that we are going to substantially
9 reduce or eliminate it.
10 The British saw a reduction of 30
11 percent between 2004 and 2005, and we forgot,
12 over the years, the experience that we had
13 with the ALT test, for instance.
14 When we introduced ALT in the
15 '80s, we didn't expect more than a reduction
16 of 20 to 30 percent in non-A, non-B
17 hepatitis, and we thought that this was a
18 great thing then, an achievement, and we were
19 able to talk about it.
20 Today, when we implement
21 regulatory measures, we think about the last
22 case that we want to prevent with either a

1 question that there's no way out, that a
2 person has to say yes or no, or if we do the
3 120 days for West Nile virus deferral, if the
4 person has--because we are looking--or in the
5 malaria question, because we are looking to
6 an absolutely black and white. And I think
7 that it would be wise, at least in the case
8 of TRALI, to think again that partial
9 measures are going to get us there.
10 We have a wish list, and the wish
11 list, some of it is happening as more
12 research. We need help from both
13 manufacturers and from FDA in terms of
14 computer software. We need faster changes,
15 because we need logistics to be able to
16 manage these donors and products and those
17 changes.
18 Most of the computer systems
19 available in the news today do not link the
20 release of a unit to the gender of the donor.
21 Yes, we can use simplified systems
22 like Dr. Benjamin proposed, or an M or an F,

1 but we need systems that are more precise.
2 For the practicing physicians we
3 need more education, we need clearer
4 definitions of TRALI and TACO, which is a
5 picture that is still confusing for many of
6 them.
7 We need better assays for
8 antibodies to HLA, and to neutrophils. We
9 need practical assays for detection of
10 biological response modifiers. There's one
11 lab in the country that does it.
12 We need practical approaches to
13 reduction of biological response modifiers.
14 We need clearly regulatory definition. We
15 heard, I was glad to hear from Dr. Williams
16 that this is under consideration by the
17 Agency, and we need also some funding for
18 hemovigilance systems, and so that we can
19 involve more, hospital involvement in
20 hemovigilance so that we can measure the
21 impact of what we do. I thank you very much.
22 DR. SIEGAL: Thank you, Dr.

1 Bianco. Are there any questions?
2 DR. EDWARDS: Maybe it's just that
3 I'm hungry but what's TACO? Willarda
4 Edwards.
5 DR. BIANCO: Transfusion
6 Associated Circulatory Overload. There's too
7 much fluid leading to the--
8 DR. EDWARDS: Thank you.
9 DR. KLEINMAN: Steve Kleinman. I
10 just wanted to make a couple comments on
11 Celso's presentation, and for the committee,
12 but not from the perspective of REDS II but
13 in my role as senior medical adviser to ABB,
14 and so I wanted to make a couple of comments
15 about the ABB bulletin.
16 And the first comment is there are
17 three recommendations in that bulletin, not
18 just one. Everybody is focused on the one
19 recommendation which says we need to find
20 ways to change the transfused component to
21 minimize risk.
22 But I can tell you, the committee

1 that formulated that bulletin felt just as
2 strongly, if not more strongly, about the
3 second recommendation in the bulletin, and
4 that is we need to get clinicians to use
5 these products appropriately and only to
6 transfuse when indicated by evidence-based
7 medical guidelines as was mentioned by Dr.
8 Sarode earlier.
9 And I was very encouraged to see
10 how much he could modify the use of FFP in
11 his hospital.
12 Now the reason we didn't make that
13 the primary recommendation is because it's
14 kind of a motherhood recommendation. The ABB
15 and Red Cross and ABC has been saying this
16 for years. We need to get clinicians to
17 minimize the use of unnecessary transfusion.
18 Unfortunately, we haven't been successful at
19 doing that nationwide, and that's why we felt
20 we needed to come up with some other
21 recommendation, we couldn't rely on that.
22 But I really want this committee to also

1 consider this as an action.
2 I don't know that FDA can have any
3 role in minimizing inappropriate transfusion,
4 but I think it's very important that we, as a
5 community, recognize that that's a prevention
6 mechanism, not just for TRALI, but for all
7 adverse transfusion reactions.
8 And so one of my comments on both
9 Celso and Richard's presentation is that as
10 their centers go out and try to educate the
11 community that FB24 is equivalent to FFP,
12 please include in your educational efforts
13 that most of the times you transfuse FFP, you
14 don't need to do it, and we have an
15 alternative product you can use, but you know
16 what? You don't really need it.
17 And I don't know if we can get
18 that into the educational message, but I
19 think it's a very important one. The second
20 point that I wanted to--and then the third
21 recommendation, which is difficult to put
22 into practice, is we need to be able to

1 monitor what's happening with TRALI as we
2 take these interventions, and that of course
3 in order to monitor cases of TRALI, we need
4 good clinical recognition, good reporting to
5 the blood bank, good reporting to the blood
6 center, and that's a whole separate topic,
7 but, you know, we shouldn't lose sight of the
8 fact that that's important. Otherwise, we
9 don't know if what we did really had a
10 positive effect.
11 The other issue I wanted to
12 address is why the ABB came out with a
13 recommendation to say that we should try to
14 do something in terms of modifying our
15 components, and I think it's all been alluded
16 to but it's worth saying again, that we had
17 to make a decision based on the best data
18 that's out there, and the data that was out
19 there was a combination of what you've heard
20 today.
21 The SHOT experience, which
22 suggests, strongly suggests, I think, that

1 making this change affects the incidence of
2 TRALI, the Red Cross experience that you
3 heard Dr. Benjamin present, which says it
4 looks like if they were not transfusing
5 female plasma, they would have prevented
6 cases of mortality, the FDA data that says
7 there's really a lot of mortality out there,
8 and then one additional item that wasn't
9 addressed today, and that is if you look at
10 the clinical series of cases of nonantibody-
11 mediated TRALI, it seems to be a much more
12 mild condition. Many fewer patients go on to
13 mechanical ventilation and the fatality rate
14 is essentially zero from nonantibody-mediated
15 TRALI, whereas for antibody-mediated TRALI, a
16 high rate of mechanical ventilation and, you
17 know, maybe a 10 percent mortality.
18 So we recognize we're not going
19 to--TRALI is multifactorial and these
20 interventions are not going to prevent TRALI
21 that comes from biological response
22 modifiers, but if, in fact, what we think is

1 true, turns out to be true, and that is that
2 the more severe cases are from antibody-
3 mediated TRALI, that's another reason to take
4 a step now and recognize that we can only
5 solve part of the problem, not all of the
6 problem, but that as Celso said, it's a
7 significant part of the problem and if we can
8 reduce TRALI, the severe cases, by 20, 30, 50
9 percent, that's a realistic goal and we
10 should take it.
11 So that's the reasoning that went
12 behind the ABB recommendations.
13 DR. SIEGAL: Thank you, Steve.
14 DR. BIANCO: I added a couple of
15 slides, at the end, that I didn't talk about,
16 that were slides about use and misuse of
17 blood products, and a few references, just to
18 encourage people to think about it just
19 following your recommendation.
20 DR. SIEGAL: Okay. I think the
21 hour is late. Dr. Epstein.
22 DR. EPSTEIN: A quick question for

1 Celso and then a quick question for Dr.
2 Stroncek.
3 For Celso, you showed on one of
4 your graphs, that centers expecting to
5 consider selection of products and donors
6 would reach 90 percent by fourth quarter of
7 07. Are we talking about predominance of
8 male plasma?
9 DR. BIANCO: Yes.
10 DR. EPSTEIN: So we'll have
11 essentially a uniform system in the country
12 by fourth quarter 07, at least--
13 DR. BIANCO: That's the hope.
14 They are trying to comply with the ABB
15 recommendation that was for November,
16 actually.
17 DR. EPSTEIN: Right. Thank you.
18 And my question for David. In
19 reviewing the available technologies, I was
20 struck by these are all detection methods,
21 and I was wondering if anybody's looking at a
22 compatibility type method, in other words,

1 where you would, you know, mix donor serum
2 with recipient cells and look for some kind
3 of reaction, presumably something related to
4 agglutination. Is that feasible? Is that
5 thinkable? Is anybody working in that
6 direction? Because it would have the
7 advantage of being testing done at the time
8 of release in the transfusion service and
9 wouldn't require a lot of prior typing work.
10 DR. STRONCEK: Nobody that I know
11 of is thinking about that. One of the issues
12 would be you're looking at--part of the
13 problem is like with red cells, the plasma is
14 diluted, and then you'd have to use cellular
15 isolation methods. Or leukocyte isolation
16 methods. But there are reagents that are
17 available, that you can isolate leukocytes
18 fairly quickly. So I guess it's feasible.
19 People just haven't really thought about
20 doing that.
21 That might be a way--agglutination
22 assays tend to pick up higher, tighter

1 antibodies, so that might be a way to only
2 screen our products that are more
3 problematic.
4 DR. KLEIN: If I could just
5 comment on that, what goes around comes
6 around, because some 30 years ago NIH did
7 precisely that with platelet transfusions
8 using a leukocyte agglutination assay, sent
9 off thousands--I should indicate that's when
10 the National Cancer Institute was running
11 transfusion of platelets and had a lot of
12 money.
13 We got a lot of data on leukocyte
14 agglutination and one of the problem is that
15 certainly by the technologies that are not
16 available, you get a lot of agglutination
17 related to HLA antibodies, and so what
18 happens is that you find a lot of individuals
19 who appear incompatible and yet there's no
20 problem when you transfuse the component.
21 DR. SZYMANSKI: About the U.K.
22 study, I'd like to ask you, those cases that

1 were not prevented by male plasma, what was
2 the reason for the death or other kind of
3 symptoms? Were they female plasmas?
4 DR. BIANCO: No. There were some
5 cases where there were HLA antibodies in
6 males and then there is a proportion of cases
7 in which no antibodies were identified and no
8 obvious reason for the TRALI could be
9 determined.
10 DR. MANNO: I wonder, Dr.
11 Benjamin, or Bianco, if there's been any
12 reinvigorated interest in solvent detergent
13 plasma, with the better understanding of the
14 pathophysiology of TRALI, and I mentioned
15 earlier that it wasn't recognized, following
16 the transfusion of SD plasma.
17 DR. BIANCO: Well, there has been
18 a substantial interest in solvent detergent
19 plasma in Europe, and to my knowledge, the
20 manufacturer in Europe, that is Octapharma,
21 is distributing over a million units a year
22 in Europe at the present time, and I know

1 that because some of our members provide that
2 plasma.
3 I think that there are other
4 issues that are not directly related to the
5 product itself, that prevent it's manufacture
6 in the United States. It's more a question
7 of manufacturers and patents than the product
8 itself.
9 DR. SIEGAL: Dr. Kleinman.
10 DR. KLEINMAN: I just wanted to
11 comment again on the question about the U.K.
12 In my understanding, their continued TRALI
13 cases do not come from high plasma volume
14 components from females. They primarily come
15 from red cells, and I don't think they had
16 any cases since they implemented their
17 female, their predominantly male plasma
18 program, and since they, a number of those
19 cases in 2004 were still caused by female
20 plasma that was collected and still in
21 inventory.
22 But I think since they've actually

1 made the change, they don't have any cases
2 from female plasma containing FFP or buffy
3 coat platelets.
4 DR. BIANCO: Yes, that's correct,
5 Steve, but the numbers are very small. They
6 went down from six to three.
7 DR. SIEGAL: We're running very
8 late, so we'll have one last comment.
9 DR. SARODE: My comment is about
10 S/D plasma in United States. I think the way
11 it was prepared is slightly different than
12 European, and we had a lot of thrombotic
13 complications because this particular plasma
14 had diffuse levels of natural coagulants and
15 there was also decreased amount of alpha-20
16 plasmin, that led to thrombotic complication
17 in patients who were getting a lot of S/D
18 plasma. So that could be a concern for
19 physicians in United States who use the same
20 product.
21 DR. SIEGAL: It's now time for the
22 open public hearing.

1 Is there anyone who wishes to
2 participate in the open public hearing?
3 [No response]
4 DR. SIEGAL: If there's no
5 one who wishes to speak, we can proceed to
6 the questions for the committee.
7 DR. WILLIAMS: Okay. So question
8 one for the committee. Do current scientific
9 data support the concept that the following
10 interventions will reduce the incidence of
11 TRALI? The first part. Use of predominantly
12 male plasma for transfusion. Second. Nonuse
13 of plasma for transfusion from donors with a
14 history of prior transfusion, and third,
15 selective donor screening for anti-neutrophil
16 or anti-HLA antibodies.
17 I was asked if this could be taken
18 as a yes/no question. I think I'd give a
19 qualified yes response to that. I think
20 there may be some variants between the
21 responses to those subsections, so if you
22 could vote those individually, and we would

1 like a sense from the committee of the degree
2 of yes-ness or no-ness with respect to their
3 value as preventions.
4 The second question is based on
5 available data. Please comment on the effect
6 on the U.S. plasma supply of the following
7 interventions, and then again use of
8 predominantly male plasma for transfusion,
9 nonuse of plasma for transfusion from donors
10 with a history of prior transfusion, and
11 selective donor screening for anti-neutrophil
12 or anti-HLA antibodies.
13 DR. SIEGAL: Okay. Do we want to
14 entertain discussion on the first question?
15 DR. KATZ: I had a question for
16 Alan, very quickly. The circular of
17 information is being revised by an
18 organizational group convened by ABB. That
19 brings FD24 and FFP into essentially the same
20 set of indications.
21 My understanding was that the
22 language had been submitted to FDA and was

1 interested in what is FDA's current thinking
2 about the equivalence or lack, or not, of
3 those two products?
4 DR. WILLIAMS: I can't comment
5 specifically because if that's under review,
6 I think it really hasn't been discussed
7 extensively internally. I think basically
8 the concept in the prior circular of
9 information, FFP, has been indicated for all
10 plasma therapies, including the labile
11 components, Factor VIII, Factor V.
12 Whether these are then being
13 modified to have the same clinical
14 indications between FFP and 8-hour product
15 and a 24-hour product I think would need to
16 be data-based.
17 DR. SIEGAL: Any other comments?
18 [No response]
19 DR. SIEGAL: Then as they say in
20 the Congress, let's have an up or down vote
21 on the first question, which is do we think
22 that scientific data support the concept that

1 the following intervention will reduce the
2 incidence of TRALI, and that's the use of
3 predominantly male plasma for transfusion.
4 DR. DI BISCEGLIE: I think I heard
5 Dr. Williams indicate that he'd be willing to
6 hear a vote on each of the three parts
7 separately.
8 DR. SIEGAL: That's what I'm
9 advocating that we do. First question. So
10 do we believe that there is enough evidence
11 for the first question? All saying yes? Can
12 I have a show of hands.
13 DR. DI BISCEGLIE: The first
14 question being what? The first part of the
15 first question?
16 DR. SIEGAL: First part of the
17 first question. Male donors.
18 I'm sorry. I didn't hear you.
19 DR. SZYMANSKI: Can we comment on
20 that issue before you take yes/no vote?
21 DR. SIEGAL: Yes. Please, no
22 filibusters.

1 DR. SZYMANSKI: No; okay; okay.
2 Listen, I think the evidence shows that the
3 male plasma is associated with a lesser
4 amount of TRALI cases. However, I think
5 there are very many good female donors that
6 should not be eliminated from platelet
7 transfusion, particularly, because otherwise
8 you have enough pheresis platelets who are
9 good donors, and they should be, you know,
10 permitted to keep donating platelets,
11 especially if they have not had a history of
12 transfusion or pregnancy, or if they are
13 totally antibody-negative. So that's my
14 qualification for that question.
15 DR. SIEGAL: Thank you, Dr.
16 Szymanski. Any other points?
17 DR. FINNEGAN: I would support
18 that comment in a Texas form, to say the
19 answer is yes but this is similar to using a
20 nuclear weapon for a fire anthill.
21 DR. KATZ: It's actually not.
22 With the conversion to--if people will accept

1 FP24, this is simple, this is a doable thing,
2 that at least the British experience suggests
3 has observable impact in a short period of
4 time.
5 DR. FINNEGAN: And I agree with
6 that but if you look at it from scientific
7 point of view, what we're doing is we don't
8 understand the problem, there's
9 pathophysiology for this problem, we have
10 only looked at one side of the
11 pathophysiology, we have no idea or very
12 little idea bout the recipient, and the
13 recipient is probably at least a reasonable
14 component of the pathophysiology and we have
15 no data on that.
16 So that, in fact, yes, it will
17 solve the problem for now, but, in fact, it's
18 going to have some secondary consequences,
19 some of which we won't be happy about in a
20 year or two, especially if we have a major
21 disaster, and we need some science on the
22 other half of the problem.

1 DR. SIEGAL: So the question is
2 whether we believe there's enough evidence to
3 support that.
4 DR. SZYMANSKI: Can we way support
5 yes, support with qualifications?
6 DR. SIEGAL: Shall we have a show
7 of hands or go around the room, do it person
8 by person? Let's go around the room.
9 DR. RIOS: So answer to 1A? Mine
10 is yes.
11 MR. JEHN: Yes.
12 Dr. Klein.
13 DR. KLEIN: Yes.
14 MR. JEHN: Dr. Nelson.
15 DR. NELSON: Yes.
16 MR. JEHN: Dr. Schreiber.
17 DR. SCHREIBER: Yes.
18 MR. JEHN: Dr. Szymanski.
19 DR. SZYMANSKI: Yes, with
20 qualifications.
21 MR. JEHN: Dr. Whittaker.
22 DR. WHITTAKER: Yes,

1 predominantly; not exclusively.
2 MR. JEHN: Ms. Baker.
3 MS. BAKER: Yes, with the
4 qualifications previously indicated.
5 MR. JEHN: Okay. Dr. Di
6 Bisceglie?
7 DR. DI BISCEGLIE: Yes.
8 MR. JEHN: Dr. Edwards.
9 DR. EDWARDS: Yes.
10 MR. JEHN: Dr. Finnegan.
11 DR. FINNEGAN: Yes, with
12 qualifications.
13 MR. JEHN: Dr. Kuehnert.
14 DR. KUEHNERT: Yes.
15 MR. JEHN: Dr. Manno.
16 DR. MANNO: Yes.
17 MR. JEHN: Dr. Siegel.
18 DR. SIEGEL: Yes.
19 MR. JEHN: Okay. And Dr. Katz, do
20 you have an opinion?
21 DR. KATZ: No. Yes, I do. I have
22 an opinion.

1 DR. SIEGAL: Okay. Let's move on
2 to the second part of the first question.
3 Is there enough evidence that the
4 nonuse of plasma for transfusion from donors
5 with a history of prior transfusion? Anybody
6 want to speak on this issue?
7 Dr. Finnegan has an opinion.
8 DR. FINNEGAN: I don't think we've
9 seen any evidence that that is in fact a good
10 way to help this problem.
11 DR. KUEHNERT: I was just
12 wondering, I mean, if there may be other
13 things that are more, that have higher
14 relationship to this. So I mean, I guess
15 that's what bothers me a little, because I'm
16 not sure this is the next strongest risk
17 factor, and so it may have some ability to
18 reduce the incidence but it wouldn't be the
19 most effective risk factor, possibly. I
20 don't know.
21 DR. KLEIN: I think we've seen
22 virtually no data to say that it would reduce

1 the incidence or the frequency, and the data
2 that we've seen related to antibodies
3 suggests that there's no significant increase
4 in antibodies. So there's virtually no data
5 to support doing anything regarding people
6 who have been previously transfused,
7 regarding TRALI.
8 DR. SZYMANSKI: Besides, usually
9 the transfusion are leuko-reduced, so you
10 don't get leukocyte antibodies that much, I
11 would think.
12 DR. SIEGAL: Are there any other
13 comments? Then let's go around the room
14 again. Don.
15 MR. JEHN: Dr. Glynn.
16 DR. GLYNN: No.
17 MR. JEHN: Dr. Klein.
18 DR. KLEIN: No.
19 MR. JEHN: Dr. Schreiber.
20 DR. SCHREIBER: No.
21 MR. JEHN: Dr. Nelson.
22 DR. NELSON: No.

1 MR. JEHN: Dr. Szymanski.
2 DR. SZYMANSKI: No.
3 MR. JEHN: Dr. Whittaker.
4 DR. WHITTAKER: No.
5 MR. JEHN: Ms. Baker.
6 MS. BAKER: No.
7 MR. JEHN: Dr. Di Bisceglie
8 DR. DI BISCEGLIE: No.
9 MR. JEHN: Dr. Edwards.
10 DR. EDWARDS: No.
11 MR. JEHN: Dr. Finnegan.
12 DR. FINNEGAN: No.
13 MR. JEHN: Dr. Kuehnert.
14 DR. KUEHNERT: No.
15 MR. JEHN: Dr. Manno.
16 DR. MANNO: No.
17 MR. JEHN: Dr. Siegal.
18 DR. SIEGAL: No.
19 MR. JEHN: Any comments, Dr. Katz?
20 DR. KATZ: No.
21 MR. JEHN: All right.
22 DR. SIEGAL: Then finally, the

1 third component of question number two, which
2 you can call read. Selective donor screening
3 for anti-
4 neutrophil or anti-HLA antibodies. Comments?
5 Dr. Schreiber.
6 DR. SCHREIBER: I think we're just
7 starting to look at some of those
8 relationships and try to understand them.
9 From what we heard, some of them are a lot
10 more complex than we think. So I would say
11 that it's just too early to tell.
12 DR. SIEGAL: Anyone else?
13 DR. KLEIN: I would agree with
14 that. I think the data that we've seen
15 suggests that neutrophil antibodies may well
16 play a role but we've also heard that the
17 tests are not yet really robust, certainly
18 not for screening purposes, and we've seen no
19 data on screening.
20 This is a compound question, of
21 course, and we've seen some data on HLA
22 antibodies but none to suggest that it's a

1 helpful technology at this point in time and
2 I suppose those data need to mature.
3 DR. SIEGAL: Okay. Do we need to
4 go around the room on this one?
5 DR. GLYNN: So could we divide the
6 question or you really want to have the anti-
7 neutrophils with the NG/HLA? It doesn't
8 matter.
9 DR. SIEGAL: I think we probably
10 have a consensus on that one without actually
11 taking a vote. Do you agree? Can we get by
12 without that? Okay.
13 Dr. Szymanski.
14 DR. SZYMANSKI: I think it's a
15 good idea, but I think we need more data,
16 more information as to what antibodies to
17 screen, and what methodologies to use. But I
18 think it is basically good idea.
19 DR. SIEGAL: Presumably we'll get
20 those data, eventually, certainly from the
21 REDS study about HLA. Okay. Shall we go on
22 to question two?

1 DR. WILLIAMS: So question two has
2 to do on the impact on supply. Based upon
3 available data, please comment on the effect
4 on the U.S. plasma supply of the following
5 interventions. And they're the same three
6 interventions. I think we'd probably also
7 welcome any comments related to apheresis
8 platelets in the same thing.
9 DR. SIEGAL: All right. We're
10 going to take this one section at a time.
11 Okay. Comments on question one, 2A?
12 DR. KATZ: Well speaking as a
13 collection facility person, a representative
14 of the industry, handled appropriately the
15 male plasma is eminently doable. The cell
16 that is required to hospitals and clinicians,
17 FP24 versus FFP, has turned out, at least in
18 my experience with 55 hospitals, to be much
19 easier than I ever thought. I was certain
20 the surgeons would tell me, when my patients
21 start bleeding FP24 I'll transfuse it.
22 And they haven't. And the data,

1 the in vitro data, it's not clinical data, it
2 isn't a clinical trial of FFP versus FP24 for
3 a variety of complex coagulation disorders.
4 But the in vitro data says the
5 level are maintained and to the degree that
6 we know what FFP does, FP24 should be
7 equivalent for almost all indications, and so
8 I think as long as we have the ability to use
9 FP24, where required logistically, it should
10 not have an important impact.
11 DR. SIEGAL: Anyone else? Harvey.
12 DR. KLEIN: I would agree with
13 that and I think in some extent it's moot,
14 because I think most of the U.S. plasma will
15 be predominantly male by the time anyone gets
16 around to making any kind of recommendation,
17 in addition to which I think that like whole
18 blood and red cells, the education will not
19 be all that difficult. We don't use whole
20 blood anymore, for very good reasons, and I
21 think we'll probably use FP24 predominantly
22 for equally good reasons.

1 DR. SIEGAL: Dr. Szymanski.
2 DR. SZYMANSKI: I think it will
3 affect the platelet availability.
4 DR. SIEGAL: Dr. Schreiber.
5 DR. SCHREIBER: I'm not convinced
6 you can separate the first and the second
7 parts. I agree that it's probably adequate
8 now, but if you do away with transfused males
9 and you drop somewhere between, I think the
10 estimate is 4 to 7 percent of the population,
11 I think we'd have a tough time filling all of
12 the plasma needs with females.
13 DR. GLYNN: But George, it's
14 predominant, it's not all. I mean, that's a
15 big difference.
16 DR. NELSON: I think the word
17 "predominant" is key here, because if there's
18 a shortage, critical shortage, it means that
19 it can be filled with a female donor.
20 DR. DI BISCEGLIE: If I might
21 comment, another factor that affects
22 availability, we've already touched on, which

1 is use or misuse. As a hepatologist taking
2 care of patients with liver disease, who have
3 coagulopathies, I'm quite comfortable with
4 the strategy outlined of not misusing plasma.
5 My problem is my colleagues.
6 If I want to get somebody to
7 operate on one of my patients, or a
8 cardiologist to do a heart catheterization,
9 they won't do it unless I fix the prothrombin
10 time. And so what I'd really like is if
11 there are guidelines widely promulgated, that
12 I can point to, to tell them to back off.
13 DR. KATZ: The Clinical
14 Transfusion Medicine Committee at ABB has
15 started the process of producing a definitive
16 guideline for the use of plasma for
17 transfusion. It's an extraordinarily complex
18 process as I know you're aware, so I would
19 guess the output's, I don't know, a year away
20 or what; but it's going to be a while.
21 DR. SIEGAL: Any other comments?
22 All right. Let's go around the

1 room again. I think on one and two, if
2 that's agreeable to people, since we've
3 discussed them both.
4 MR. JEHN: Dr. Glynn.
5 DR. GLYNN: I'm sorry. We have to
6 vote on this? Exactly what kind of vote?
7 DR. SIEGAL: All right. So we
8 don't have to vote. Okay; fine. So then
9 we've commented.
10 So let's go to question three, or
11 2C. Again, it's the selective donor
12 screening for antibodies.
13 DR. FINNEGAN: I think once the
14 technology's there, that's going to be the
15 answer for helping solve the problem, but I
16 still reiterate that we need to figure out
17 what the recipient's problem is as well as
18 what the donor's problem is.
19 DR. KLEIN: I think that the data
20 are clearly too immature to make much more
21 comment than to say if one wanted to screen
22 for anti-HLA antibodies, it would be a very

1 big problem in terms of the availability of
2 plasma. So again, you could divide those,
3 and say for anti-neutrophil, that you
4 probably can't do it, but it wouldn't be a
5 big problem for HLA antibodies. With the
6 current technology you could probably do it.
7 You wouldn't get much benefit and you'd lose
8 a lot of plasma.
9 DR. SIEGAL: All right. Dr.
10 Schreiber.
11 DR. SCHREIBER: Actually, I think
12 that if we had adequate technology, we might
13 be adding back a significant portion of the
14 women. As Steve Kleinman said, if we're
15 running about 30 percent, or so, elevated
16 HLAs, and that's for the whole population,
17 and we're getting rid of 50 percent of the
18 donors that are women for the plasma, we
19 might have a net gain of 25 percent.
20 DR. KLEIN: I think you're assuming
21 that HLA is actually related, and I would
22 point out that in the large study that was

1 quoted by
2 Palthey, et al, it was predominantly women
3 who'd have multiple pregnancies; it was
4 multiparous women. And they didn't look for
5 antibodies. So I'm not sure that that's what
6 we want to hang our hat on. I'd like to wait
7 for the data on that one.
8 Maybe we're looking at the wrong
9 antibodies by the particular technology that
10 we're using.
11 DR. SCHREIBER: I agree. I think
12 we really need the data, but I think we might
13 be pleasantly surprised.
14 DR. SIEGAL: Are there any other
15 comments?
16 [No response]
17 DR. SIEGAL: In that case let's
18 declare this session over and we'll reconvene
19 in 45 minutes. Is that agreeable to
20 everyone?
21 [Whereupon, a luncheon recess was
22 taken from 12:33 p.m. to 1:18 p.m.]

1 **A F T E R N O O N   S E S S I O N**

2 DR. SIEGAL: Okay. Let's start.
3 Do we have a quorum? Probably not. Okay.
4 Topic three. Issues related to
5 implementation of West Nile virus testing.
6 We're first going to have an update on West
7 Nile epidemic 2006, by Dr. Eileen Farnon from
8 the Centers For Disease Control and
9 Prevention.

10 DR. FARNON: Good afternoon and
11 thank you for inviting me to speak today.
12 I'll be presenting an update on West Nile
13 virus epidemiology in the United States from
14 1999 to 2006.

15 West Nile virus is a mosquito-
16 borne flavivirus that is transmitted in an
17 enzootic cycle between bird and mosquitoes.

18 It causes epizootics in which
19 birds and mammals are affected by bridge
20 mosquitoes. Horses and humans are usually
21 considered "dead end" hosts because they
22 don't develop a high enough viremia to infect

1 mosquitoes, and thereby they don't perpetuate
2 the cycle.
3 This maps shows the approximate
4 global distribution of West Nile virus.
5 Prior to 1999, West Nile virus was found
6 predominantly in parts of Africa, Asia and
7 Europe, with the closely related Kunjin virus
8 occurring in Australia.
9 In 1999, West Nile virus was
10 introduced into North America and since then
11 has been found in parts of Central and South
12 America.
13 Human disease has been detected in
14 the Cayman Islands, Mexico, El Salvador and
15 Argentina.
16 CDC developed ArboNET, the U.S.
17 arboviral national electronic surveillance
18 system, in 2000, in response to the 1999
19 detection of West Nile virus in the U.S., in
20 New York City.
21 ArboNET is a passive surveillance
22 system that collects data on West Nile virus

1 and other domestic arboviral infections in
2 humans, as well as ecologic data regarding
3 infected mosquitoes, birds and other animals.
4 The information that I'll cover
5 today is based on reports to ArboNET and all
6 the data are current as of April 12th, 2007.
7 The human West Nile virus
8 syndromes reported to ArboNET include West
9 Nile fever, West Nile neuroinvasive disease,
10 including meningitis, encephalitis, and acute
11 flaccid paralysis, and other clinical
12 syndromes, as well as unspecified illness.
13 This series of maps shows West
14 Nile neuroinvasive disease incidence by
15 county in the U.S. from 1999 to 2006.
16 Neuroinvasive disease incidence is
17 thought to reflect the burden of human West
18 Nile virus disease more accurately than total
19 case counts since West Nile fever reporting
20 varies widely from state to state.
21 Counties highlighted in green on
22 these maps had ecologic activity in

1 mosquitoes, birds, or animals, and the dots
2 represent incidence per million of West Nile
3 neuroinvasive disease in humans.
4 In 1999, West Nile virus was first
5 recognized in the U.S. in the outbreak in New
6 York City. In 2000, there were cases found
7 in neighboring states. In 2001, West Nile
8 neuroinvasive disease incidents increased in
9 the Northeast and spread to the Southeast.
10 In 2002, high West Nile
11 neuroinvasive disease incidence was seen in
12 Central, South-Central and Western Plains
13 states. In 2003, the highest incidence was
14 seen in the Western Plains states.
15 The incidence in 2004 was lower
16 overall but continued to be high in the
17 South-Central, Central and Western states,
18 and increased in the Southeast and along the
19 West Coast.
20 In 2005, incidence increased in
21 the South-Central, Central and Western Plains
22 states.

1 In 2006, incidence increased again
2 and remained highest in the South-Central,
3 Central, and Western states.
4 This map shows the cumulative West
5 Nile virus activity and human cases by
6 county, from 1999 to 2006. Counties that had
7 nonhuman West Nile virus activity are
8 depicted in blue and counties with human
9 cases are depicted in red.
10 All of the Lower 48 states have
11 had evidence of ecologic West Nile virus
12 activity and only Maine, Hawaii and Alaska
13 remain free of human cases.
14 Since 1999, almost all counties in
15 the Lower 48 state have reported some West
16 Nile virus activity, sparing only a few
17 counties which are mostly in the Northwest.
18 The onset of human West Nile virus
19 cases in the U.S. has changed from 1999 to
20 2006. The West Nile virus season has
21 steadily lengthened, and in 2005, and 2006,
22 the dates of onset of human disease span

1 almost the entire year, from early January
2 until mid December, with states in the South
3 having the longest West Nile virus season.
4 We wanted to see whether some
5 states have had persistently high incidence
6 of West Nile neuroinvasive disease over the
7 past five years, to see whether there might
8 be "hot spots" of West Nile virus activity in
9 humans.
10 This map shows the cumulative
11 incidence of West Nile neuroinvasive disease
12 by county in the U.S. from 2002 to 2006, with
13 the red counties having the highest
14 cumulative incidence and the letter color
15 counties have lower cumulative incidence.
16 Harding County, South Dakota, has
17 the highest cumulative incidence of 241 per
18 100,000. Twenty-five counties in six Western
19 states have a cumulative West Nile
20 neuroinvasive disease incidence of over 100
21 per 100,000.
22 Nicole Lindsey, in our group at

1 CDC, recently examined how many of the
2 counties with high cumulative West Nile
3 neuroinvasive disease incidence also had
4 consistently high annual rates of West Nile
5 neuroinvasive disease incidence, and
6 therefore might be "hot spots" where West
7 Nile virus activity may continue to be high
8 in the future.
9 This is a scatterplot that
10 compares the median annual West Nile
11 neuroinvasive disease incidence rank with the
12 cumulative West Nile neuroinvasive disease
13 incidence rank for each country from 2002 to
14 2006, in order to determine whether counties
15 with high cumulative incidence had
16 persistently high annual incidence in the
17 five years from 2002 to 2006.
18 Since some counties have very few
19 West Nile neuroinvasive disease cases and
20 small populations, Nicole limited the
21 analysis of county incidence to 447 counties
22 where the cumulative incidence rate was,

1 where the 95 percent confidence interval for
2 the cumulative incidence rate was more than
3 zero.
4 This plot shows that most counties
5 did not have consistently high annual
6 incidence. There were only a few counties
7 that were "hot spots," shown in red, orange
8 and light blue, with high cumulative
9 incidence and persistently high annual
10 incidence. Most counties with high
11 cumulative incidence had only one or two
12 years with high annual incidence, which can
13 be seen at the end of the x axis. Over
14 there.
15 This analysis also indicates that
16 counties that have had low incidence of West
17 Nile virus transmission, in dark blue, over
18 here, tend to maintain low transmission
19 rates.
20 Looked at geographically, this map
21 shows the "hot spot" counties with
22 persistently high West Nile neuroinvasive

1 disease incidence from 2002 to 2006. The
2 counties in the top 5 percent of both
3 cumulative and median annual incidence for
4 West Nile neuroinvasive disease are shown in
5 red, the ones in the top 10 percent in
6 orange, and the ones in the top 20 percent in
7 light blue.
8 These "hot spot" counties cluster
9 in the Western Plains states and at the
10 eastern edge of the Rocky Mountains, with a
11 few in the South-Central states.
12 This chart summarizes the total
13 reported West Nile disease cases in humans in
14 the U.S. from 1999 to 2006.
15 The columns show the total number
16 of cases, West Nile neuroinvasive disease
17 cases, West Nile fever or other cases, and
18 deaths, and the rows show the year.
19 The number of human cases reported
20 to ArboNET peaked in 2003, declined by almost
21 a fourth in 2004, and have been increasing
22 again, for a total of 4,261 human cases

1 reported in 2006 to ArboNET, and almost
2 24,000 cases, to date, since 1999.
3 The need for West Nile virus blood
4 screening became apparent in 2002, when 23
5 cases of West Nile virus transfusion-
6 associated transmission, or TAT, were
7 documented. In 2003, FDA initiated screening
8 of the blood supply with nucleic acid
9 amplification test or NAT. Mini-pool NAT or
10 MP-NAT is done on pools of samples of six to
11 sixteen units, and units from positive units
12 are then tested individually by individual
13 NAT or ID-NAT. Blood banks report
14 presumptively viremic donors or PVDs, to
15 local health departments and remove infection
16 blood products from circulation.
17 Public health departments then
18 report these cases to ArboNET, perform
19 clinical follow-up on the cases, and perform
20 traceback investigations along with partners
21 including blood banks, tissue banks, organ
22 procurement organizations, and FDA, as

1 appropriate, in order to identify other
2 potential cases infected by the same donors.
3 This chart shows the number of
4 West Nile virus presumptively viremic donors
5 by year. In 2003, after screening of the
6 blood supply for West Nile virus began, 818
7 donors were identified, followed by 224 in
8 2004, 417 in 2005, and 361 in 2006. A total
9 of 1820 PVDs have been identified by this
10 system over the past four years.
11 This map shows the number of
12 presumptively viremic blood donors by their
13 state of residence in 2006. These numbers
14 correlate fairly well with the states that
15 had the highest incidence of neuroinvasive
16 disease cases in 2006.
17 Over 8 million blood donations
18 were screened for West Nile virus in 2006.
19 Of the 361 PVDs reported to ArboNET in 2006,
20 23 percent developed West Nile fever, 0.1
21 percent developed West Nile neuroinvasive
22 disease, and 0.1 percent developed other

1 unspecified illness from West Nile virus
2 infection.
3 These percentages are similar to
4 those seen in West Nile virus serosurveys.
5 33 percent of the PVDs reported in
6 2006 were from three states--Nebraska, Idaho
7 and Texas. Two suspect cases of West Nile
8 virus transfusion-associated transmission
9 that occurred in 2006 were found to originate
10 from a donor whose multiple NAT screen was
11 negative.
12 The blood bank testing his
13 donation had not yet reached their trigger
14 for ID-NAT, although other blood banks had
15 also found PVDs around the time from the same
16 region.
17 The first case was an 82-year-old
18 male resident of South Dakota who had
19 recently received a kidney transplant. At
20 four days, post transplant, he received two
21 units of packed red blood cells. At 21 days
22 post transplant, he developed encephalitis.

1 West Nile virus IgM was detected in his serum
2 and CSF.
3 Pre-mortem serum from the organ
4 donor tested negative for West Nile virus by
5 serology and PCR. The recipient of the organ
6 donor's other kidney was asymptomatic. and
7 his serum, post transplant, tested negative
8 for West Nile virus infection. The case
9 patient had also received blood products from
10 six different donors before he developed
11 encephalitis and all six donors were tested
12 for West Nile virus infection.
13 One of the blood donors was
14 positive for West Nile virus IgM. He was
15 from rural South Dakota and had been
16 asymptomatic before and after donating blood.
17 His sample had tested negative for
18 West Nile virus RNA by multipool NAT. A
19 traceback investigation of this blood donor
20 revealed that a second immunocompromised
21 patient had also likely been infected by a
22 donation from the same donor. Fresh frozen

1 plasma from his donation had been transfused
2 into a 60-year-old male resident of Iowa who
3 was five years post-kidney transplant.
4 He had undergone a spinal fracture
5 repair in South Dakota and received 15 blood
6 products, including six units of FFP from the
7 West Nile virus infected blood donor.
8 Eleven days, post-operatively, he
9 developed encephalomyelitis and West Nile
10 virus IgM was detected in his CSF.
11 Both of these cases are considered
12 to be suspect cases of West Nile virus
13 transfusion-associated transmission. Both
14 had been hospitalized for at least to weeks
15 before the onset of West Nile neuroinvasive
16 disease and were unlikely to have acquired
17 the disease via mosquito bite. These cases
18 were described in an MMWR article that was
19 published in February, which discussed the
20 issue of how ID-NAT triggering mechanisms
21 differ across the U.S.
22 The occurrence of these cases

1 indicates that despite enormous successes in
2 screening the blood supply for West Nile
3 virus, it may be possible to improve on
4 current triggering mechanisms.
5 This could be approached by
6 examining how different triggering methods
7 would have worked, using either existing data
8 or using theoretical models of West Nile
9 virus outbreaks.
10 In summary, West Nile virus
11 transmission now occurs throughout the
12 continental United States. States and
13 counties in the Western Plains and the
14 eastern edge of the Rocky Mountains seem to
15 have the highest incidence of West Nile
16 neuroinvasive disease.
17 The dates of onset for human West
18 Nile virus disease now span almost the entire
19 year. Two cases of transfusion-associated
20 transmission occurred despite multipool-NAT
21 testing in a region where PVDs were diagnosed
22 simultaneously by separate labs.

1 Because of these cases, new
2 approaches to triggering ID-NAT are being
3 considered in order to further lower the risk
4 of transmitting West Nile virus through the
5 blood supply.
6 I would like to thank the
7 following people and organizations for their
8 assistance providing the data I presented
9 today. Thank you.
10 DR. SIEGAL: Thank you very much.
11 Are there any questions for Dr.
12 Farnon?
13 DR. NELSON: I was interested that
14 23 percent of the people have fever.
15 Presumably this was fever that occurred after
16 the donation, because they would have been
17 excluded from donating if they had a fever at
18 the time of donation. Is that correct?
19 DR. FARNON: That's absolutely
20 correct. They should be excluded, if they
21 had a fever at the time. I'm not entirely
22 certain about last year's numbers. I know in

1 the past, there have occasionally, in
2 published reports, been cases of people who
3 donated despite having had a recent history
4 of fever, and so hopefully at this point, all
5 of the cases that subsequently, all of the
6 PVDs subsequently developed fever before or
7 on the day of their donation. I don't have,
8 unfortunately, that information.
9 DR. SIEGAL: Harvey.
10 DR. KLEIN: Is there any
11 speculation as to why West Nile seems to have
12 settled into the Western states where you
13 showed the prevalence for a couple of years
14 now?
15 DR. FARNON: Right. Especially in
16 the Western Plains states, there's a lot of
17 irrigation of large plots of land for
18 agriculture, and it's thought that that kind
19 of practice actually is sustaining the
20 epidemic in those areas. So particularly,
21 say, Nebraska and so on.
22 DR. NELSON: Have vectors been

1 studied as well in that area, because I
2 think, as I understand it, Culex tarsalia is
3 much more of a human pest, biter, human only,
4 and I wonder does this explain it or--
5 DR. FARNON: That is also one
6 theory, that Culex tarsalia is a more
7 aggressive human biter than pipiens in the
8 Northeast, say. Again this is a theory and
9 we like to latch on to it, but from what I
10 understand from entomologists, it seems more
11 likely that just the agricultural practices
12 and topography of the land, and so on, may be
13 playing more of a factor than the mosquito
14 itself.
15 Obviously, there are a number of
16 different factors that play into this and
17 it's complicated to figure out what the
18 reasons are.
19 DR. SIEGAL: Yes, Dr. Szymanski.
20 DR. SZYMANSKI: A question. How
21 long after infection does the NST test remain
22 positive and when do the antibodies appear?

1 DR. FARNON: I'm sure there are
2 people in the audience who could respond to
3 this better than I can. I believe the NAT
4 test itself can--although live viremia, in
5 terms of virus isolation is thought to last
6 on the window of, say, three to five days,
7 maximum, the NAT test can remain positive for
8 much longer than that, up to I think about
9 two or three weeks.
10 DR. RIOS: It has been found up to
11 104 days, positive. 104 days. That's the
12 extreme end of the--but within a month or two
13 will still be positive.
14 DR. SIEGAL: Any other questions?
15 Thank you very much, Dr. Farnon.
16 DR. KLEINMAN: Will you take some
17 from the audience?
18 DR. SIEGAL: Yes; sure.
19 DR. KLEINMAN: I have two
20 questions. The early onset cases in the
21 early part of the year, prior to April, can
22 you give us, in the last two years, can you

1 give us some idea of how many cases come on
2 in the first quarter and where they're from
3 and how well-documented they are.
4 DR. FARNON: Sure. They do tend
5 to be well-documented, because generally
6 speaking, the first cases of the year attract
7 some attention, both at the state health
8 departments and at the CDC, and we believe
9 that they are true cases, confirmed cases.
10 Mostly in the Southern states are where you
11 will see the first cases of the year, and
12 it's varied from year to year. One year, the
13 first case was found in LA County and one
14 year it was in Texas.
15 So this year, we may be having our
16 first cases now in Mississippi but, generally
17 speaking, there are all these in the South of
18 the U.S.
19 DR. KLEINMAN: Okay. And my other
20 question. Have people at CDC speculated as
21 to what they might expect for 2007?
22 DR. FARNON: People like to say in

1 arbovirology that you never really know what
2 to expect. But that being said, I think
3 that's part of the reason why they wanted to
4 do this study that I presented, that Nicole
5 Lindsey did, looking at "hot spots," and I
6 think the feeling is that the highest
7 incidence areas will remain in the Western
8 Plains states and possibly increase in the
9 West Coast as well.
10 But that being said, we all think
11 that West Nile virus is now endemic
12 throughout the U.S., throughout the Lower 48
13 states.
14 DR. SIEGAL: Okay. Let's move on.
15 Thank you. The next speaker is Maria Rios,
16 PhD, of FDA, speaking on issues for testing.
17 Dr. Rios.
18 DR. RIOS: Thank you, and after
19 Eileen's presentation, my presentation will
20 be actually much better, much clearer, I
21 hope, and I will be talking to you about
22 issues related to implementation of blood

1 screening for infection with West Nile virus.
2 FDA seeks comments from the
3 committee on issues to implementation of
4 donor screening with NAT for West Nile virus
5 with regards to screening itself, additional
6 testing, and donor counseling, and that's
7 what we would like the committee to discuss.
8 As Eileen already posed the
9 background, West Nile was identified as a
10 threat to the blood supply in August 2002,
11 and efforts among DHHS agencies and test kit
12 developers and blood establishments led to
13 the rapid development and implementation of a
14 nationwide screening under FDA-approved IND
15 in July 2003.
16 So was nine months, exactly, as
17 she stated, after the initial identification
18 of a threat, West Nile is a threat, and
19 today, this number is higher than what report
20 in CDC because CDC reporting is lagging
21 behind. It's done through the State
22 Department. But we know that it's over 2000

1 units that have been intradicted due to the
2 West Nile reactivity in the United States.
3 And that may have led to the
4 prevention between of 2000 and 6000 potential
5 transmission by blood transfusion since the
6 implementation of ID--oh, since the
7 implementation of NAT under IND.
8 In this slide, what I wanted to
9 point out to you is that since 2002, there
10 have been increasing number of cases of
11 neurological disease, and as Eileen pointed
12 out, it started very low and it peaked in
13 2002 to 2003, and since 2002 there has been
14 higher than one thousand cases of
15 neurological invasion of West Nile, and at
16 least a 100 deaths, and more.
17 Based on the estimation made by
18 CDC, early estimation that one in a 150
19 infections will lead to neurological invasive
20 disease, and more recent data published in
21 2006 with new data collected during this
22 testing period, that one in every 350

1 infections will end up causing neuroinvasive
2 disease. We can estimate that it has been in
3 the lower end at 1.5 to 3.5 million
4 infections in the U.S. during the last eight
5 consecutive years.
6 So West Nile epidemic has
7 reoccurred, causing almost 24,000 human
8 disease and almost one thousand deaths, as
9 shown by Eileen. These titers of assays
10 since implementation, FDA license in 2002,
11 the first NAT for volunteer donor screening
12 in its Procleix assay, manufactured by Gen-
13 Probe and distributed by Chiron, and in March
14 2007, FDA licensed the first fully automated
15 system for volunteer blood donors screening,
16 and it's the Procleix assay running the
17 TIGRIS system manufactured by the same
18 manufacturers and distributions. Alternate
19 assays are currently under IND.
20 You have seen this, Eileen showed
21 you, and this slide she kindly provided me
22 last year, and it's just to show that from

1 1999 the awareness grow, growth of awareness,
2 the identification of human cases of West
3 Nile increased. So did the extent of the
4 epidemic. So now we have year-round human
5 infections which is sustaining 2006.
6 So we know that it's from January
7 of December. So West Nile became endemic in
8 the U.S. with peak during spring to fall, and
9 it's a reportable disease to the CDC, and
10 since 2002, we have observed that there have
11 been higher than 1000 cases of neuroinvasive
12 disease, meaning encephalitis, meninges
13 encephalitis, and the meningitis and the
14 acute flaccid paralysis, and this makes a
15 parallel with the Japanese encephalitis in
16 the Far East, that has been for many decades
17 causing at least a thousand encephalitis in
18 the Far East.
19 And we also have seen that there
20 have been at least a 100 fatalities a year
21 since 2002.
22 So it is an issue. FDA is

1 considering whether or not--whether blood
2 establishments should screen West Nile by
3 minipool NAT year round, because we have seen
4 activity from January to December. With the
5 begotten test, in two thousand--this was
6 already mentioned to you--but in 2003, six
7 cases of West Nile transmission after
8 minipool tests and these units were tested as
9 negative by minipool NAT and they were
10 transfused and transmitted the infection.
11 Retrospectively, studies were performed and
12 voluntarily by blood establishments, and they
13 observed that 75 percent of the infectious
14 units would be detected but 25 percent of
15 units would be undetected.
16 That led to the voluntary
17 implementation by the blood centers in 2004
18 of ID-NAT, which would be used in individual
19 donating testing, which would be used in
20 areas during the peak epidemic with high West
21 Nile activity, that led to additional
22 identification of units that wouldn't be

1 detected in minipool NAT and increase the
2 safety of the blood supply. And the same was
3 used in 2005.
4 So ID-NAT was implemented based on
5 the criteria that the most common was one in
6 a thousand reactive donation, or two minipool
7 reactive or positives a week, whichever would
8 come first during the epidemic.
9 You're going to see these models
10 from Dr. Stramer, that will be in the next
11 presentation. So since selecting ID-NAT,
12 there have been three confirmed cases of West
13 Nile transmission by transfusion. One was in
14 2004. There had been no cases documented in
15 2005, but I want to remind you that we don't
16 test all the blood recipients. In West Nile,
17 not a 100 percent of cases will cause
18 symptoms.
19 So in the--two cases in 2006. So
20 FDA is considering, we are considering
21 whether blood establishments should implement
22 ID-NAT in areas with high West Nile activity

1 and uniform criteria to initiate ID-NAT is
2 desirable, and there is a fully automated
3 system licensed right now. However, there is
4 a paucity of data to define unifying criteria
5 for search implementation of uniform ID-NAT.
6 The AABB has voluntarily
7 recommended they publish the position and
8 it's published in the Bulletin 0702, if
9 anybody wants to take a look at it, and we
10 are considering whether blood establishments
11 should define and validate criteria to
12 trigger ID-NAT and to revert back to minipool
13 NAT when the peak season is passed.
14 The current algorithm used is that
15 the blood donations are pooled into six or
16 sixteen minipools, depending on the kit
17 manufacturer, and if the minipool tests
18 negative and the units are suitable for
19 transfusion, then they are released for
20 transfusion.
21 If the minipool NAT is reactive,
22 then each one of the units that compose the

1 minipool is tested individually to identify
2 the unit or units, or specimens that led to
3 the pool reactivity.
4 Once that you identify that the
5 unit's negative by ID-NAT, if suitable, they
6 are released, and the ones that are reactive,
7 they are discarded, donor-deferred for 120
8 days, and additional tests are performed with
9 the purpose of counseling.
10 These additional tests are repeat
11 the NAT, either using the same NAT that was
12 used for screening or an alternate NAT with
13 greater or equal sensitivity of the screening
14 assay, and to perform West Nile antibody or
15 presence of antibody to West Nile virus.
16 I would like you to note that
17 flavivirus family has high rate of cross-
18 reactivity among the various members.
19 In studies that soon we will
20 release for you, that has been collected by
21 the blood agency, has shown that a
22 combination of a repeat NAT plus presence of

1 antibody has a positive predictive value of
2 98 percent and sensitivity of 98 percent, and
3 she will give you details of this.
4 So we are considering whether
5 blood establishments should retest donation
6 by ID-NAT, using either the same screening
7 assay or an alternate NAT of equal or higher
8 sensitivity, and test ID-NAT initial reactive
9 donations by antibody to West Nile virus.
10 I would like to call your
11 attention again that antibody for West Nile
12 virus can cross-react with other flavivirus
13 and vice-versa.
14 With regard to additional test, if
15 a NAT assay is specific for flavivirus but
16 not for West Nile, discriminatory of West
17 Nile, we are considering whether blood
18 establishments should perform West Nile
19 specific discriminatory assay in order to
20 determine West Nile virus infection.
21 In the case of additional testing,
22 as I mentioned to you before, the minipool

1 NAT is tested by individual donations
2 testing, and the individual, the reactivity
3 of the individual donations are repeated by
4 ID-NAT using the same alternate assay and
5 antibodies performed.
6 If these initial reactive repeat
7 positive, then the specimen is considered
8 positive and the donor is considered
9 positive, regardless of antibody result.
10 But if the antibody is present,
11 and both are present, then it's clear that
12 it's antibody to West Nile or at least to the
13 flavivirus and you consider the donor
14 positive.
15 However, if the NAT is nonreactive
16 but the antibody's positive, then you would
17 consider positive based on the antibody and
18 the same thing with the antibody negative but
19 not reactive.
20 These specimens which are ID-NAT
21 reactive and the repeat, and the repeat NAT
22 is nonreactive, and the antibody are absent,

1 it's considered false positive or meaning
2 through negative. However, Susan will show
3 you these data again, that 2 percent of the
4 true positive on follow-up are actual, the
5 false positive are actually true positive
6 upon follow-up.
7 And overall, close to 10 percent
8 of the initial repeat NAT, that it's
9 nonreactive in the repeat NAT, they are true
10 positive based on antibody test.
11 So we are considering whether it
12 is appropriate initial reactivity specimen
13 not be regarded as false positive based
14 solely on negative test results on additional
15 testing in the index donation, regardless of
16 the NAT to antibody solely, or whether it's
17 appropriate for a donor to be considered true
18 positive based on repeat reactive NAT, or
19 West Nile antibody positive.
20 And again I would like to call
21 attention that the assays, they will not
22 discriminate between West Nile and other,

1 Japanese encephalitis, other group of virus.
2 It's not really appropriate to consider
3 these individuals as true positive for West
4 Nile virus.
5 Regarding donor counseling, due to
6 the potential for false negative result, it
7 is desirable to inform donors with initial
8 reactive ID-NAT about the possible infection
9 with West Nile virus. Donors with initial
10 reactive ID-NAT may be counseled and invited
11 for follow-up test performed using ID-NAT and
12 antibody assays, at least 30 days after the
13 initial reactive donation.
14 And initial reactive ID-NAT
15 donations may not be released for transfusion
16 and donors should be deferred for 120 days.
17 We are considering whether it's
18 appropriate that container label and
19 instruction circular to reflect the results
20 of West Nile NAT, consistent with labeling
21 for infection disease markers, and also West
22 Nile reactivity units not to be shipped or

1 used except as provided in FDA-approved
2 program and/or research, autologous use only.
3 And such units should be labeled
4 with appropriate warnings.
5 With regard to donor deferral and
6 reentry, product retrieval and recipient
7 notification, we are considering maintaining
8 the recommendation as is stated in the June
9 2005 guidance, which is in the Web site.
10 Thank you.
11 DR. SIEGAL: Thank you.
12 Questions?
13 Well, I have a question, just to
14 ask you a couple of things. The total, the
15 epidemiology of this virus is that it's
16 infected over a million people in the United
17 States.
18 DR. RIOS: I'm sorry. I didn't
19 hear you.
20 DR. SIEGAL: It's quite prevalent,
21 this virus. You go outdoors and you get
22 bitten by the wrong mosquito, and you're

1 likely to get infected, and looking at the
2 epidemic spread and the wave-like process
3 that took us across the United States and the
4 very low prevalence now, makes me think
5 probably there's a lot more prevalence to
6 this virus and it actually may have saturated
7 the population to some extent.
8 Well, even so, if there are, say,
9 2 million people infected in this country,
10 how many transmissions have we had by blood
11 transfusion?
12 DR. RIOS: We don't know. We know
13 confirmed, documented cases. We don't know
14 how many transmissions there has been,
15 because not all West Nile infection cause,
16 lead to infec--to serious outcome or
17 symptoms, and also we don't know if one unit
18 is not detected as positive because of the
19 limited detection of the assay, would cause
20 some mild febrile symptom that can be
21 considered as normal reaction for
22 transfusion.

1 So, in fact, we don't really know.
2 We have--what we don't, we can't prove, is
3 how many really are, and we know which ones
4 were documented but we don't know how many
5 there were in fact.
6 DR. SIEGAL: Well, what I was
7 getting at is just to play the devil's
8 advocate, if it's so easy to get infected in
9 the ambient environment, relatively speaking,
10 and there's an awful lot of transmission
11 going on anyway, and most of the people who
12 are getting this are the "canaries in the
13 mine," the immunocompromised hosts that have
14 clinical manifestations. Maybe it isn't
15 justified.
16 If you look at Mike Bush's
17 analysis of cost-effectiveness, to spend all
18 the money that it costs to interdict the few
19 transmissions by blood transfusion, when the
20 virus is out there anyway.
21 DR. RIOS: I understand and I
22 agree with you, but the public health issue

1 is to prevent transmission by transfusion to
2 people that need to be taken care of.
3 DR. KUEHNERT: I just wanted to
4 say that I think if you want to look at the
5 number of transfusion transmissions that
6 likely occurred before screening, it would be
7 best to look at the models rather than the
8 actual cases that were reported, cause, you
9 know, there's a definition that needs to be
10 met, and, you know, all the hurdles that we
11 talked about for all the other diseases we've
12 talked about at this meeting.
13 But anyway, you know, either the
14 model is wrong and there are less cases, or
15 there's massive underreporting, and that's
16 what we think is going on. If there are 23
17 cases in that first year, and, you know, I
18 think the modeling suggested hundreds or
19 thousands. I can't remember the exact
20 numbers now.
21 I guess what I'm saying in answer
22 to--I mean, I think you're trying to get at

1 what the utility of the test is and looking
2 at cost and benefit.
3 DR. SIEGAL: What's the
4 incremental benefit that society will have
5 compared with the natural vector
6 transmission?
7 DR. KUEHNERT: And for that I
8 think you really have to try to estimate what
9 the actual number of transmissions are.
10 Otherwise, you're starting from a--it's a
11 false premise.
12 DR. SIEGAL: Just thought I'd ask.
13 DR. DI BISCEGLIE: I think I'm
14 missing something in what you're asking us.
15 I've seen the phrase used, to trigger ID-NAT,
16 but I don't know what that means, and as a
17 sort of part of that question I think, can
18 you tell us the absolute sensitivities,
19 approximately, of the assays NAT used in
20 screening, and then you alluded to more
21 sensitive assays.
22 DR. RIOS: What I can tell you is

1 that since the identification, or the finding
2 that only 75 percent of the infected units
3 were detected in the minipool, and the
4 limitation of availability of reagents at
5 that time, and logistics at the blood centers
6 and automation, etcetera, we knew that the
7 viral load in West Nile is not so high that
8 the pooling, unlike HAV and HCV would much be
9 affected, West Nile has a lower viral load.
10 So what I'm calling the trigger is
11 what would tell people to please start
12 testing because human cases are rising in
13 these particular area anyway, and what has
14 been in the news and was a volunteer
15 determination from blood centers that have
16 done a series of studies--and Susan will
17 address that I hope--if not, if you could
18 please--is that when they see one reactive
19 unit in a thousand, they implement ID-NAT in
20 that particular region because West Nile is
21 very focalized. It's not spread.
22 Regionally, it's very localized and actually

1 they can pinpoint area of activity. Pockets.
2 Or having too many pools reactive
3 and then they start doing ID-NAT, and that's
4 what we say trigger, is to start the
5 implementation of ID-NAT instead of
6 minipools.
7 DR. DI BISCEGLIE: And that's
8 permanent thereafter or it's for the rest of
9 that season, or what?
10 DR. RIOS: But that's why I said
11 we hope to have the blood centers validating
12 their implementation, reverting back for
13 minipool, and what has been used to revert
14 back, Susan will approach, but it's one week
15 without any reactive and they go back. But
16 Susan will give these detail.
17 DR. NELSON: In areas where
18 there's epidemic, there'll be a certain
19 proportion will have a very low level of
20 viremia, so they go from the pools of six to
21 sixteen down to a single donation, hoping to
22 pick up those with lower levels, which would

1 still transmit a virus if it was transfused.
2 And the trigger now is one in a
3 thousand or two minipool NATS in a week.
4 DR. RIOS: Reactive.
5 DR. NELSON: In what, a county?
6 In a county or a state or a city, or what
7 geographic--
8 DR. RIOS: I would like Susan to
9 address that because this is their algorithm
10 for triggering.
11 Dr. Nakhasi--
12 DR. NAKHASI: I just wanted to
13 make some clarification about the trigger, a
14 little bit. You know, as Maria pointed out,
15 that even though these assays are very
16 sensitive, some of them are, you know,
17 approximately ten copies per mL detection,
18 there are, you know, even at--the viral load,
19 as such, for West Nile is much, much lower,
20 so with minipool you may miss some of them
21 and that's why you need to trigger that to
22 ID-NAT and what the trigger, which was--you

1 know--because as we were testing them, blood
2 establishments wanted to find out, you know,
3 to catch all those cases, most of the cases,
4 so they arbitrarily, depending upon, on this,
5 so one in thousand or two in minipool,
6 meaning two minipool NATs in a particular
7 area, it was started, and turned out to be
8 that, you know, in 2005, there were none, in
9 2004 there was one case. However, as you saw
10 in 2006, in spite of that trigger there were
11 two cases which held true.
12 So the question is do we need to
13 really tighten that trigger and I think Sue
14 will tell you some of the studies, what can
15 be done to tighten that trigger. And also
16 you have to remember that it doesn't remain
17 permanently.
18 If the blood establishments don't
19 see for seven days, continuously, no positive
20 in that area, they will revert back to
21 minipool NAT testing.
22 DR. RIOS: Dr. Nakhasi, I would

1 like to just make a correction, that the
2 claim for the assay is a 100 copy per ml.,
3 not 10 copy per ml.
4 DR. NAKHASI: Yeah. I know the
5 claim is different but it can detect as low
6 as ten.
7 DR. DI BISCEGLIE: And what's the
8 level of infectivity? What's the amount of
9 viremia that we think is infectious, or--
10 DR. RIOS: This is not known and
11 the reason is because we would need NHLBI to
12 fund as a study of effectivity, and to define
13 what is the viral load required for
14 infection. As you know, when the
15 concentration is low in one area, and you use
16 a small animal, you cannot simulate a human
17 blood transfusion.
18 We know that units that have been
19 detected, or tested nonreactive in minipool,
20 were capable of transmitting infection to the
21 recipient.
22 DR. NELSON: Presumably, if it's

1 transmitted by a mosquito bite, if you find
2 any in a unit of blood you're going to
3 probably transmit it, I think, if there's any
4 virus there.
5 DR. KUEHNERT: I just wanted to
6 just clarify. I'm hearing two cases in 2006
7 and it was two infections from transfusion
8 transmission but it was from one donor.
9 DR. RIOS: I agree, Matt, but if a
10 mosquito bite, two people, it's two
11 transmission. It's not one mosquito only.
12 DR. KUEHNERT: Right; right. It's
13 two transmission from one--but it's one
14 minipool NAT. That's the only point I was
15 making.
16 DR. KLEIN: But Matt, if I
17 understand it correctly, the second recipient
18 who had meningeal encephalitis, would not
19 have been detected without the look-back. In
20 other words, they would not have known that
21 this was due to West Nile, which again goes
22 to the issue of it's probably underreported,

1 because you would guess that something as
2 impressive as encephalitis would not go
3 underreported, but clearly it does because
4 people don't think of West Nile.
5 DR. KUEHNERT: You're absolutely
6 right, and also that these happen to be two
7 transplant recipients who are at manyfold
8 greater risk of developing complications and
9 these complications were so unusual, that it
10 prompted the clinicians to seek out--the one
11 clinician to seek out why it happened.
12 The others, it still did not
13 prompt an investigation until the look-back.
14 So I think those are points well-taken.
15 DR. SIEGAL: Any other questions
16 for Dr. Rios? In the back. Okay. Then I
17 think we have come to Dr. Stramer, data in
18 support of the current ID-NAT triggers,
19 American Red Cross again.
20 DR. STRAMER: Good afternoon. I'm
21 back. So to continue along the presentations
22 that have already been made by the CDC and

1 FDA, this is like the blood center rebuttal,
2 or whatever, I'm covering two major areas.
3 One is West Nile confirmation, which we
4 really need to understand for appropriate
5 donor counseling, and this will be based on
6 data that we collected nationally from the
7 periods of time, from 2003, when testing
8 began, through 2005.
9 And then also data in support of
10 West Nile ID-NAT triggers, as advertised in
11 the agenda.
12 The first series of slides comes
13 from an AABB presentation that has been
14 modified for the use in this presentation,
15 and also through the work of the West Nile
16 Task Force, which is a small group from the
17 blood centers who work through the AABB. It
18 also includes AABB staff, members from the
19 FDA and members of the CDC.
20 So we have gone through all of the
21 concepts that I will be presenting to you.
22 So this should not be new to many

1 individuals, but anyway. So this first
2 portion deals with confirmation. So just to
3 give the committee some background, donor
4 screening for West Nile RNA by NAT began in
5 June 2003, prior to the onset of the national
6 epidemic for that year, and we all heard
7 about the magnitude of the 2002 epidemic and
8 the short period of time it took for test
9 kits to be developed and implemented.
10 During 2003 through 2005, all
11 blood programs in the United States performed
12 investigational NAT for West Nile in
13 minipools, or individually, designated as MP
14 or ID, during the epidemic periods and in
15 epidemic locations.
16 And we converted from minipool to
17 ID-NAT, which was dependent on site-specific
18 triggers. We already mentioned that there
19 were a number of triggers used through the
20 United States. But, for example, one such
21 trigger, as Maria mentioned, was two positive
22 cases and a frequency of one in a thousand

1 positive donations, and I'll go through the
2 derivation of the triggers and
3 standardization of the use of triggers in
4 later slides.
5 For this particular portion of my
6 talk, three blood collection testing programs
7 contributed data, which represented greater
8 than 80 percent of blood collected in the
9 United States, or over 4 million donations
10 per West Nile season, and covered all
11 geographic regions.
12 And even though West Nile testing
13 occurs throughout the year, in all U.S.
14 areas, to focus on incidents and new cases
15 reported each year, this report covers only
16 the epidemic periods of the mosquito season
17 for a given year.
18 And that's defined as the date of
19 collection between the first and last West
20 Nile confirmed positive blood donor.
21 The screening tests used were
22 either the Gen-Probe test, as I describe on

1 this slide, or the Roche test, which I'll
2 describe on the next slide.
3 Gen-Probe, which is now FDA
4 licensed on both platforms, that is, their
5 semiautomated platform and an automated
6 platform, was used by some participants in
7 the study. The test is distributed by
8 Chiron, it's transcription mediated
9 amplification, which is an RNA amplification
10 system, in minipools of sixteen, using
11 either, as I said, the semiautomated or the
12 TIGRIS system, both of which are now FDA
13 licensed.
14 The sites included the American
15 Red Cross, United Blood Services, and all
16 contract facilities for both of those blood
17 systems, and it represented again all
18 geographic areas within the United States.
19 The second test used was the Roche
20 investigational test. This is in minipools
21 of six, using the Taq screen, that's the
22 commercial name of the test, and it included

1 the 12 sites that are listed here. I will
2 read them. They're listed in your handout.
3 For confirmation, which is a
4 really important component of this talk, TMA
5 or PCR, depending on the test, if they were
6 initially reactive, they were considered
7 confirmed positive, if they met one of the
8 following criteria.
9 If the initial test repeated as
10 reactive in the original or modified test
11 format, and a modified test is called
12 Alternate NAT or ALT NAT, and preferably,
13 this was from an independent sample from the
14 index donation, such as I talked about
15 yesterday from the retrieved plasma unit.
16 The index donation tested West
17 Nile antibody that is IgM, or IgG positive,
18 and the way the sites use antibody testing
19 was program dependent. There was a test
20 available from Abbott laboratories for the
21 first year, Focus has tests, and the Safe
22 Public Health Labs also do antibody testing.

1 And the other criteria for confirmatory was
2 if the donor follow-up samples were tested
3 and they were reactive by either repeat NAT,
4 that is, TMA and/or PCR or antibody.
5 And in most programs, if we did
6 have a positive PCR, that was followed by a
7 quantitative test that was performed at
8 National Genetics Institute.
9 This is the results of the first
10 three summers of testing. So this includes a
11 total of 13 million donations.
12 The number of donations that were
13 screened during this period of time,
14 individually, were 3.8 percent--actually,
15 there was some individual donation testing
16 that we performed in 2003, when we realized
17 quite a large local epidemic in Nebraska and
18 Kansas. So that total percent is 4 percent.
19 These are the date ranges. So pretty
20 reproducible form--this was the earliest
21 year, the beginning of May, but we've seen
22 cases all the way through the end of the

1 November into the first day of December was
2 our last case.
3 So what the data set will now
4 focus is on the 1329 confirmed positives. So
5 if you look at the frequency for 10,000
6 donations overall, we see a frequency of one
7 in ten thousand, which is actually ten times
8 higher than the one in one thousand trigger
9 that we'll talk about.
10 And here on the bottom we just
11 show the CDC numbers in comparison. I
12 mention this is only about 80 percent of
13 collected blood in the United States
14 contributed data to this study, so this is
15 consistent with what was reported to CDC
16 which should be all.
17 When did West Nile occur in those
18 three years? This is the epidemic curve,
19 showing you 2003, the beginning. The upslope
20 of the epidemic and then the tailing through
21 the first week of December. Then 2004 came
22 up a little bit earlier, and 2005 actually

1 came up a little bit later. 2006 was
2 somewhere between 2003 and 2005 and isn't on
3 this map.
4 Where West Nile occurred, you
5 already heard that in the first presentation
6 from CDC, but again, in this corridor that's
7 east of the Rocky Mountains, where we see the
8 highest number of cases, we've also now seen
9 in the last couple of years very high numbers
10 in the state of California.
11 So the increasing color here
12 indicates numbers that are increasing and the
13 numbers in the states obviously indicate the
14 number of positive donors.
15 So in Nebraska, for example, we've
16 had 298 viremic donors that have been
17 identified.
18 Looking at the characteristics of
19 these 1329 donations, if you start from the
20 earliest period of time, these are those
21 donations that are ID-NAT reactive only,
22 followed by those donations that could be

1 detected by minipool, obviously would be ID-
2 NAT reactive as well, but the difference here
3 is these are ID-NAT only, minipool NAT
4 negative. Then we have minipool NAT
5 positive, both cases being antibody negative.
6 Then with the appearance of antibody, we
7 still have donations that are detected by
8 minipool and are antibody positive. But then
9 we have this long tail of donors that are
10 detected only by ID-NAT, that have antibody.
11 So if you look at the data in
12 aggregate, and look at those donations for
13 which triggering is important, that's the top
14 row and the bottom row, that total is, as
15 Maria said, about 25 percent, but in this
16 study of all of our data for the first three
17 years, it turned out to be 22 percent of NAT
18 reactive donations required ID-NAT for
19 detection.
20 That is, if we maintain minipool
21 NAT, those would not be detected.
22 Also if you look at the difference

1 in antibody positivity, the vast majority, or
2 I should say three-quarters of what we see
3 are antibody negative donations versus 26
4 percent that are antibody positive. The
5 smallest percentage here being minipool, NAT,
6 and antibody test positive for this category.
7 If you now look at viral loads,
8 which are indicated on the x axis here again-
9 -this is from the National Genetics
10 Institute--and you divide the samples into
11 those that are antibody negative and antibody
12 positive, you can see, in red, these are the
13 antibody positive samples.
14 The antibody positive samples have
15 the lowest viral loads, as I showed on the
16 prior graph, that more of the antibody
17 positives are detected by ID versus minipool
18 NAT.
19 Only 76 percent of the total had
20 adequate volume and went through the
21 algorithm for quantitative testing. But in
22 any event, you can see that the large numbers

1 of antibody negative donors here have the
2 highest viral loads.
3 But even so, the highest viral
4 load of any sample detected was only 580,000
5 copies, which is considerably lower than what
6 we see for HIV or HCV, which is why, for West
7 Nile, we have to have a strategy of ID-NAT
8 triggering as opposed to just minipool NAT
9 testing because we would miss a considerable
10 number of donations.
11 So one can think of minipool NAT
12 as kind of a surveillance system until the
13 epidemic hits, and then we convert to ID-NAT.
14 If you now look at all donations
15 that were detected and divide them into both
16 minipool reactive and individual donation
17 reactives, but look at those that are false
18 positive versus those that were confirmed
19 positives, and then look at the signal-to-
20 cutoff ratios, which everyone, as I said
21 yesterday for Chagas, everyone wants to know
22 what the meaning of a signal-to-cutoff ratio

1 is.
2 For those that confirm positive by
3 minipool, which are in red, those are the
4 highest signal-to-cutoff ratios. Those that
5 are confirmed positive but were only detected
6 by ID-NAT, as I showed you in the prior
7 slide, have lower viral load, so their
8 distributions across the S to CO values are
9 much broader.
10 And if you look at an S to CO
11 value in the case of the Gen-Probe test which
12 we use, at least at the Red Cross, and blood
13 systems that is predictive for whether a
14 sample will confirm, we use an S to CO of
15 seventeen, and we have found that 88 percent
16 of those samples that have an S to CO equal
17 to or greater than seventeen will confirm.
18 So it's very useful as we identify
19 NAT-reactive donors. In contrast, the false
20 positives all have low S to CO values, and
21 they're comprised of those to be detected,
22 either ID-NAT or minipool NAT.

1 And the algorithm we use
2 specifies, if an ID-NAT result is positive,
3 we take actions on the donor and the
4 products, versus minipool NAT where you have
5 two rounds of testing before you do doom a
6 donor, so to speak.
7 So both the minipool and
8 individual donation NAT have to be positive.
9 So if you just base positivity on one test
10 result, we're obviously going to see more
11 positive hits with ID-NAT than minipool NAT.
12 So one of the downsides of triggering and
13 converting to ID-NAT is we lose more donors
14 because each ID-NAT reactive is a deferred
15 donor, and their products are destroyed.
16 Looking at false positive across the three
17 years of study, I think the individual years
18 is not what is necessarily important, but the
19 bottom line message here is that 70 percent
20 of what we see for false positives, as I just
21 mentioned, occurred during the ID-NAT season,
22 and the frequency of false positives,

1 overall, is .55 per 10,000 donations.
2 So 500 of 722 false positives seen
3 in the three years were detected during the
4 ID-NAT season, or as a consequence of
5 triggering. Now focusing on the confirmed
6 positives, I've divided them in different
7 colors here. So the first column here,
8 before we go through the rows, is
9 seroconversion of follow-up. How many donors
10 were followed through follow-up and confirmed
11 as positive?
12 The other criteria here, these now
13 represent the index donation--how many were
14 antibody-positive at index, either by IgM or
15 IgG? And then the other index criteria is
16 how many showed repeat reactivity by the
17 same, or an alternate NAT at index donation.
18 So these reflect what we did at index versus
19 donor follow-up.
20 So of the 200 in this category
21 here, that were confirmed as repeat reactive,
22 and indexed by alternate NAT, for most, we

1 didn't have a follow-up sample. But in the
2 further slides where I'm going to talk about
3 positive predictive value, etcetera, we would
4 consider six of these eligible to go on for
5 further study, because they did show RNA
6 positivity at follow-up, so we could
7 reproduce the fact that they were West Nile
8 infected in a subsequent sample.
9 Now looking at either NAT
10 reactivity at index in the presence of
11 antibody, or NAT reactivity at index in the
12 presence of antibody--these are addended
13 index, so these are antibody-positive at
14 index, split into NAT-positive at index or
15 NAT-negative at index. We have the two
16 numbers here but those that will go into
17 further study are 83 and 156. So of these
18 128, we followed 83, and all 83 had zero
19 converted. So we will carry these numbers on
20 into further calculations.
21 Of the 217 that did confirm by two
22 independent methods of index, at follow-up

1 156 of those followed did zero convert. So
2 in each of these cases, one could argue you
3 could take all of these, because we had a 100
4 percent agreement between those in these
5 categories that were confirmed by follow-up.
6 But for the purposes of analysis, we will
7 deal with these six, this 83, this 156, and
8 then we come to these yellow boxes.
9 Here we have donations who did
10 seroconvert on follow-up. This first
11 category here is those that were antibody-
12 negative or NAT-negative at index. So for
13 these ten donors, as Maria already mentioned,
14 the only way that we confirm them as positive
15 was by follow-up. So these would represent
16 false negatives at index and influence the
17 sensitivity of the confirmatory algorithm.
18 These 764 that were repeat NAT-
19 reactive at index also seroconverted. So
20 again, these will be the numbers that we take
21 through
22 on the next slide.

1 So now looking at the calculations
2 of how good a confirmatory algorithm is,
3 based on index testing and/or follow-up
4 testing, we have no donors who were confirmed
5 positive in index, as I indicated on the
6 previous slide, but were not antibody-
7 negative at--but were antibody-negative at
8 follow-up. We had ten in the category I just
9 showed you, that were confirmed only by
10 follow-up testing, and were negative at
11 index.
12 Then, if you added the six, if you
13 add all of these numbers together that I
14 indicated, you come up with 1009. So these
15 were the confirmed positive at index, and we
16 confirmed them again at follow-up to
17 corroborate the index test results. And then
18 I showed you the 540 false positive results,
19 and these were based on negative results at
20 follow-up and these individual donors.
21 So these 1009 split into the two
22 groups that I showed you, 239 that were

1 confirmed at index based on antibody and
2 antibody at follow-up, and the 920 of the
3 larger group that were confirmed positive at
4 index based on repeat NAT and antibody.
5 So going through the various
6 calculations, firstly, we have 1019 confirmed
7 positives over the 1559 initial reactives.
8 That's all comers. So the positive
9 predictive value of the screening assay is 65
10 percent. The negative predictive value here,
11 how many of these false positives were over
12 the denominator of total reactives, for which
13 we need a follow-up to resolve, there were
14 540 over 550, adding in these ten, so we have
15 a negative predictive value of the screening
16 test of 98 percent.
17 And then based on the positive
18 predictive value of index confirmation, all
19 of these 1009 that were confirmed at index
20 also were confirmed at follow-up. So our
21 positive predictive value was 100 percent.
22 Sensitivity, we did have the ten false

1 negatives, so that drops that to 99 percent.
2 Sensitivity of repeat NAT, which is this
3 calculation over the 1019, 90 percent, and a
4 sensitivity of antibody at index is 23
5 percent.
6 So overall, the sensitivity of
7 index confirmation is 99 percent but it's
8 made of these two components. You can just
9 repeat NAT for 90 percent sensitivity or you
10 can do antibody as well, to increase that or
11 get the extra 20 percent, which, because
12 there's overlap, this adds up to 99 percent.
13 Now one question that we ask is,
14 well, some people repeat the same NAT method,
15 or some use an alternate NAT method. Is
16 there a difference in sensitivity?
17 So of the 1196 samples that were
18 tested at index by both a primary and an
19 alternate NAT, here we had 86 percent
20 detection, or 86 percent detected with the
21 alternate NAT assay, and about 87 percent
22 actually no significant difference between

1 these numbers by the primary NAT assay.
2 And the discordance solves the
3 vast majority of these were antibody-positive
4 anyway, so even if you use only one NAT,
5 rather than using two NATS, we have the
6 benefit of doing the antibody test, which
7 we'd recommend that you do both repeat NAT
8 and antibody. So we would recommend only one
9 NAT test, their primary or alternate be
10 adequate.
11 So what do we conclude from this?
12 The positive predictive value of the
13 screening algorithm, as I mentioned, 65
14 percent, indicates the need for confirmatory
15 testing, and I did mention the 69 percent of
16 false positives drive the lower PPV obtained
17 during the periods of ID-NAT. The positive
18 predictive value of our index donation
19 confirmatory algorithm was a 100 percent,
20 using follow-up as our gold standard. All
21 donors who were confirmed positive based on
22 the index donation results have been

1 accurately classified as West Nile infected,
2 that is, no false positives were observed.
3 The sensitivity of the
4 confirmatory algorithm based on the index
5 samples testing approximates that based on
6 follow-up testing, indicating very little
7 additional value is obtained by follow-up
8 testing. I showed you a 99 percent
9 sensitivity that was divided into 90 percent
10 by repeat NAT only, and 23 percent, if you
11 add the antibody--well, 23 percent alone by
12 antibody, giving you a total of 99 percent.
13 Now if you balance this against
14 follow-up, the disadvantage of follow-up is a
15 confirmatory algorithm, as we've seen,
16 requiring follow-up testing, will never have
17 100 percent sensitivity, in practice, because
18 not all donors will participate in follow-up.
19 And then lastly, the few true
20 positive donors who would not be classified
21 as confirmed positive based on the index test
22 results, would already have been counseled

1 for possible West Nile infection. They have
2 been deferred for 120 days and components
3 from their donations would have been
4 quarantined. Thus, there is no adverse
5 impact on blood safety by eliminating follow-
6 up testing.
7 Now let me switch to triggering.
8 The need to trigger, that is, convert from
9 minipool testing to ID-NAT, during epidemic
10 periods, is based on the low viral loads that
11 we have discussed for West Nile as compared
12 to HIV or HCV.
13 I mentioned the 22 percent of West
14 Nile NAT-positive samples detected required
15 ID-NAT for detection. Or another way of
16 saying this, or looking at the data, where
17 the 26 percent of the detected samples were
18 antibody positive, of which the majority, 81
19 percent, required ID-NAT.
20 Most systems have implemented some
21 type of trigger, it's not standardized, no
22 method exists for site-to-site communication.

1 So triggering has been successful; however,
2 as we've heard, there have been two West Nile
3 breakthrough cases that occurred in 2006, and
4 these numbers you've seen before, so I'll
5 skip ahead.
6 So based on--I say "need for
7 improvements," I should say that in quotes,
8 we can always make improvements. But based
9 on the two cases that we saw in 2005, the
10 AABB West Nile Task Force that I mentioned
11 already, representing the blood industry,
12 developed an association bulletin that was
13 released on April 3rd. We did receive input
14 from the CDC and FDA on that bulletin, and
15 the recommendations involved the use of a
16 minimum trigger that has been shown to be
17 feasible and has relatively high
18 effectiveness.
19 And a comparison of multiple
20 triggers were published by Brian Custer and
21 his co-workers at Blood Systems and
22 Transfusion in 2004. We first validated this

1 triggering algorithm by 2002 retrospective
2 studies, based on the frequency of West Nile
3 clinical disease, which was one in a 1000 in
4 the 2000 year, and the observation of one
5 minipool negative unit for four minipool NAT-
6 positive units that we observed in those
7 retrospective studies, and those data were
8 published.
9 So what did we say in the
10 association bulletin? We recommend a
11 minimum criteria based on initial reactive
12 donations and rapid time to respond, that is,
13 within 24 hours, due to the short duration of
14 the ID-NAT-only- window period. And for ID-
15 NAT, that's about two days. The entire
16 minipool NAT window period is about seven
17 days. And after seven days without seeing a
18 repeatable ID-NAT reactive, or an antibody
19 positive, sites can revert back to minipool
20 testing.
21 The other portion of the
22 association bulletin focuses on a

1 communication plan and a communication plan
2 based on the existing testing sites that have
3 entered data already into the AABB Web site,
4 and therefore have had communication plans in
5 place for their institutions and their
6 customers.
7 So institutions already have such
8 communication plans, but what we don't have
9 is communication between facilities. So
10 contact information and states for which
11 collected donations are tested is provided as
12 an attachment to the association bulletin.
13 Sites for which collections occur
14 in adjacent or overlapping areas should be
15 communicating. That's what we're trying to
16 accomplish. And there are many tools for
17 tracking activity. You can use your site-
18 specific data, the data that's entered into
19 the West Nile map that's on the West Nile
20 biovigilance map. That's on the AABB Web
21 site, and those donors are entered by
22 residential zip code. Maps provided by the

1 CDC. CDC reports of avian and mosquito
2 activity.
3 So all of these factors should be
4 used in determining whether you trigger or
5 not. But once you met the minimum criteria,
6 which I'll describe, triggering is required.
7 So these tools can be used, as I said, as
8 part of planning activities within facilities
9 and between facilities.
10 I plan on sending out a weekly
11 "blast" e-mail, actually, to all the
12 facilities that share our borders, to
13 facilitate easier communication this year, so
14 it won't be just within the Red Cross.
15 So the minimum criteria, I'm going
16 to describe those now, they have to be
17 feasible or they won't be done. They have to
18 be realtime, because as I said, the ID-NAT
19 window period is only about two days. It's
20 based on two West Nile NAT reactives and a
21 rate of one in a thousand, and then we've
22 gone into some further criteria to define, if

1 sites have lower numbers of collections, how
2 they should be tracking their rates.
3 Also, as far as defining a
4 geographic area, it's really impossible or
5 impractical to say it's within a zip code or
6 within a county. So the way that we have
7 defined geographic areas is by the number of
8 collections per--what's feasible is the
9 number of collections.
10 Some facilities segment their
11 facility into quadrants, so that they don't
12 have to trigger within the entire facility.
13 But we've said if your number of collections
14 is low, that's really not advised. And then
15 we recommend growing periods of time for
16 calculating rates, depending on your
17 collection numbers, or another method of
18 doing this is just to monitor between your
19 first and second NAT reactive, and trigger if
20 less than 2000 collections have occurred
21 between that interval.
22 So, again, there are just a number

1 of tools available, clinical cases by county,
2 clinical, or avian cases reported by CDC.
3 Again, clinical cases, West Nile-presumed
4 viremic donors, presumptive viremic donors,
5 and then we have the AABB tool, which is the
6 most useful tool, because it's updated, at
7 least last year, weekly. We're going to try
8 to update this more frequently this year.
9 Donors are entered by zip code.
10 So for last year, and all the maps for 2006,
11 we see 439 confirmed positives. We had 64
12 false positives. We also track by date, when
13 donations occurred. This is again on the
14 AABB Web site. We provide site-specific
15 information. This is the Red Cross map for
16 2006.
17 So actually to tie this up, or to
18 conclude, the logistics, West Nile ID-NAT is
19 a balance between sensitivity and capacity.
20 The largest labs may have capacity for a
21 thousand samples per day or 1200 samples per
22 automated instrument per day, but of course

1 that involves that the sites may have to have
2 multiple instruments and it assumes that the
3 instruments are working all the time, which
4 they're not when they're constantly
5 challenged with the high number of samples.
6 Reagent performance issues or
7 other sources of false positivity may cause
8 sites to artificially trigger early, or
9 extend the time of ID-NAT which is
10 problematic. So with that, I just show you
11 that ID-NAT and a blood system, year round,
12 does occur for multiple regions. This is
13 Nebraska, the site that we trigger every year
14 in, and we see prolonged West Nile activity,
15 and just as an example, for last year we did
16 135,000 individual donation tests during the
17 West Nile season.
18 So with that I'll conclude and
19 answer any questions. Thank you.
20 DR. SIEGAL: Thank you, Dr.
21 Stramer. We're open for questions.
22 DR. KATZ: Sue, can you talk about

1 the two ends of the ID-NAT windows and where
2 transmission occurs, the ramp-up and the
3 AMBI-positive.
4 DR. STRAMER: Well, all of the
5 cases we have seen of the twenty-three, and
6 the subsequent nine cases, have been in
7 antibody-negative individuals, and that's the
8 shortest period of time, that's the two-day
9 window, versus that longer tailing period
10 that Maria said can extend up to 104 days.
11 When we've looked at, at least for
12 Red Cross data, viral clearance occurs for 99
13 percent of individuals at 56 days, but as
14 we've observed from blood system studies,
15 they did have one donor that went out to 104
16 days. None of those--we're not saying that
17 those aren't capable of transmission, but
18 none of those have ever been implicated in
19 transmission.
20 So the prolonged, or the tail-end
21 of the ID-NAT trigger period, it's important
22 that we're able to get out of ID-NAT

1 triggering promptly, without prolonging it
2 for extensive periods of time due to false
3 positives.
4 Lou, is that kind of what you
5 wanted me to address?
6 DR. SZYMANSKI: I'm interested as
7 to what the ID, the individual testing, NAT
8 testing, is more often false negative. Does
9 it mean that the material there is in a
10 lesser strengthen than that of the true
11 positives, and therefore it's diluted better
12 in the minipools? And what would that
13 material be?
14 DR. STRAMER: Okay. I tried to
15 explain it but let me do this again. When we
16 do minipool testing, if you've a positive
17 result we do resolution testing, which means-
18 -
19 DR. SZYMANSKI: [inaudible]
20 DR. STRAMER: Right. So by
21 statistics, false positives, which are random
22 events, may occur, let's say, at a rate of

1 one in ten thousand. So you have a one in
2 ten thousand event happening at a minipool
3 stage. So then, when you do resolution
4 testing, that one in ten thousand event would
5 have to happen again.
6 So statistically, if something's a
7 false positive, it's very unlikely that it
8 would repeat two times in one, for one
9 donation. So if we have an ID-NAT positive,
10 that one in a thousand event once, that
11 defers the donor.
12 DR. SZYMANSKI: But what is that
13 material that gives the false positive? Do
14 you know what--
15 DR. STRAMER: Pardon?
16 DR. SZYMANSKI: What kind of
17 material is that, that reacts in that, you
18 know, individual, for false positive?
19 DR. STRAMER: Why it's false
20 positive?
21 DR. SZYMANSKI: Yes. What
22 material is it? Is it something--

1 DR. STRAMER: Oh, I see what
2 you're saying. The way we perform the NAT
3 tests, although many of them are automated,
4 what happens with NAT, unlike serological
5 tests in which we have biological false
6 positives, in NAT, we have, unfortunately,
7 contamination, and that's the cause of false
8 positives.
9 Whether it's from a strong
10 positive contaminating an adjacent sample due
11 to aerosolization, or less likely due to
12 external controls, or the assay calibrators,
13 although those are much lower viral load
14 samples. But if there's one high titer
15 sample, very frequently you can trace
16 neighboring samples that have been
17 contaminated.
18 DR. SZYMANSKI: Okay; thank you.
19 DR. STRAMER: And it doesn't
20 matter how good the technique is, there's
21 always going to be false positives with NAT.
22 DR. KLEIN: West Nile virus

1 testing has really become an industry. I
2 mean, there are meetings, and there are all
3 kinds of communications, and triggering
4 mechanisms. It really is pretty complex. I
5 could understand that in the days when it was
6 semiautomated, but now, with automated
7 technology, I know issues of logistics and
8 cost are the main drivers, but it seems to me
9 that there must be an argument for simply ID
10 testing across the country.
11 You've gone pale.
12 DR. STRAMER: No; my pocketbook--
13 well, the Red Cross's pocketbook has gone
14 pale.
15 DR. KLEIN: So perhaps we should
16 know what the tradeoffs would be. Is it only
17 money, or are there other--
18 DR. STRAMER: Well, it's certainly
19 false positives, loss in donors, and it's a
20 temporary loss in donors. Donors can come
21 back at 120 days. We do follow-up testing at
22 donor request, but it's certainly the loss of

1 associated products. Cost is certainly a
2 giant issue. Even though we have automation
3 of ID-NAT triggering, we still have a
4 capacity within each blood center, that even
5 if we have multiple instruments, we sometimes
6 have to balance tests between other labs to
7 balance our capacity.
8 So even with automation at 1200
9 samples per day, if we have multiple regions
10 trigger within one area, such as Nebraska,
11 Kansas, Oklahoma, you know, all that area,
12 we've exceeded the capacity of that
13 particular lab, and we would need probably
14 two or three times the number of automated
15 instruments to do this continuously, year
16 round.
17 And I would argue what the benefit
18 is, because I believe--or the data
19 demonstration that the ID-NAT triggers,
20 although there are limitations, and that we
21 did have two cases this year--or two cases
22 this past year, I believe the system is

1 pretty sensitive, and if we watch it
2 carefully, and are able to communicate and
3 use multi-site triggers, there is no reason
4 that this can't be almost, well, close to the
5 sensitivity of ID-NAT year round.
6 In the association bulletin, we
7 also mention validations, that, actually, FDA
8 recommended that we put in there, that some
9 sites validate the use of this multisite
10 trigger, and triggering just in general, to
11 see how sensitive, and if there were prior
12 donations that were missed. So with some of
13 our regions, we're going to trigger early,
14 let's say after one NAT reactive, to see what
15 we would have missed between the threshold of
16 one and two, to try to answer the question,
17 Are we missing anything? and, really, what
18 the benefit of year-round testing would be.
19 DR. SIEGAL: Dr. Rios.
20 DR. RIOS: Yes. I would like to
21 ask you to comment on your false-positivity
22 slides, that you had ten samples that did not

1 repeat NAT. Nevertheless, you considered
2 them as positive. If you would have applied
3 your algorithm that you need either
4 transmission or repeat NAT, and not perform
5 follow-up, how would you have identified, if
6 had ten additional cases that were true
7 positive and would have been considered false
8 negative?
9 DR. STRAMER: Well, these donors
10 are deferred, and in our materials we do tell
11 donors that--we counsel them such, that the
12 possibility of West Nile infection cannot be
13 excluded, and we do invite them, if
14 interested, into follow-up.
15 So all of the follow-up that
16 you've seen was voluntary, and our system, we
17 won't change that, but yes, there is that
18 chance, that if those ten donors didn't come
19 in for follow-up, yes, we would have missed
20 them. But in our counseling materials, we
21 don't tell anyone that you're unequivocally
22 uninfected, for any agent.

1 DR. KUEHNERT: How do you know
2 they weren't otherwise infected in the
3 interim, between the time of donation and
4 follow-up for the ten? Was that a--
5 DR. STRAMER: They were IgM
6 positive, relatively short--in a short
7 interval after their viremic donation. Our
8 follow-up is pretty rapid, within one to two
9 weeks.
10 DR. KUEHNERT: Okay.
11 DR. SIEGAL: Dr. Epstein.
12 DR. EPSTEIN: While we're on these
13 ten confirmatory false negatives, have you
14 been able to figure out why it happened? In
15 other words, is it correlated with low titer
16 in the index sample? Is it correlated with
17 the relative sensitivity of the secondary
18 NAT?
19 In other words, were you using the
20 original NAT? Were you using the alternate
21 NAT? Were you using a different
22 manufacturer's NAT? Etcetera, etcetera,

1 etcetera. Because one of the puzzlements
2 here is you found those samples from minipool
3 screening. They were initial reactive on ID-
4 NAT--
5 DR. STRAMER: Well, those ten were
6 actually from ID-NAT.
7 DR. EPSTEIN: Okay. Well, that's
8 another important point. Okay. So the
9 question is do we know the attributable
10 cause?
11 DR. STRAMER: Well, and actually,
12 the way we were doing index testing, we were
13 not only repeating the same NAT but we were
14 also doing alternate NAT. So in this case,
15 the index not only scored negative when we
16 did--I mean, it was initially reactive when
17 we did primary screening, but then, on
18 retesting, it was nonreactive by the same
19 method, an alternative NAT method, and
20 antibody.
21 So the only thing I can attribute
22 it to is the one out of twenty. It was just

1 the luck that we found it, because these are
2 such low level due to stochastic.
3 DR. EPSTEIN: So another way of
4 looking at it, this is that the--
5 DR. STRAMER: A chance effect.
6 DR. EPSTEIN: --negative
7 predictive value of the confirmatory
8 algorithm is higher on samples that are found
9 first on positive minipool than on samples
10 that are found first on IDT NAT, and the
11 reason is obvious. It's because you have the
12 ability to pick up lower-titered samples by
13 IDT NAT.
14 But, you know, if you were to
15 stratify it, in other words, if you were to
16 do that calculation for the ones found first
17 by minipool versus the ones found only by
18 IDT, you'd come up with a different set of
19 answers for the predictive values of the
20 algorithm.
21 DR. STRAMER: That's true. I
22 mean, are you saying you want me to--well, we

1 can look at those. We could look at that
2 calculation.
3 DR. EPSTEIN: I mean, I think the
4 results are very impressive and I'm not
5 quarreling with them at all. I'm just trying
6 to understand what we know and what we don't.
7 DR. SIEGAL: Dr. Finngean.
8 DR. FINNEGAN: Can I ask you what
9 you think it would do to your bottom line, if
10 we followed up on Dr. Klein's suggestion, but
11 instead of doing it universally, that you did
12 it during the endemic period in those
13 counties where you know you have a much
14 higher risk, and dropped it down to the first
15 positive case or one in five hundred instead
16 of one in a thousand.
17 DR. STRAMER: Well, actually, one
18 in a thousand is more sens--yes; right.
19 Well, I think, you know, what I tried to say
20 in the last slide that I had with text was
21 we've got to balance the logistics with the
22 sensitivity, and I think for this season--

1 well, I know for this season we're going to
2 keep it as we have and then look at several
3 regions that we know trigger each year, and I
4 will trigger those early, like Nebraska,
5 Kansas, and we'll look at what would happen
6 if we instituted a more sensitive trigger,
7 that was, as I said, an FDA request to
8 validate, in a way, the use of this, and the
9 only way to do that is to do more individual
10 donation testing to determine what we're not
11 picking up. So we will look at it in a
12 validation mode, but until we see data that
13 supports that, I don't think we're ready to
14 convert to a more sensitive trigger criteria.
15 I think what we need to do first
16 is convert the entire country to a
17 standardized trigger criteria and to make
18 sure that we're all communicating, so that if
19 I have one NAT reactive and you have one NAT
20 reactive, and we're collecting in the same
21 region, at least we know that together we
22 trigger, and that's the kind of data that

1 would have prevented, if we lived by lessons
2 learned, that would have prevented the two
3 transmissions in 2006.
4 DR. SIEGAL: Are there any other
5 comments?
6 DR. DI BISCEGLIE: You may not be
7 able to answer but maybe Dr. Farnon can. The
8 donors begin to be positive at the beginning
9 of May and go through the first week of
10 December. But we heard from the CDC, that
11 there are cases being diagnosed in every
12 month of the year.
13 So why the disconnect?
14 DR. STRAMER: We don't see
15 positive blood donors--I mean, one limitation
16 may be minipool testing. Not to contradict
17 the CDC, but the one from California, the
18 first case in January of last year turned out
19 to be--unless we're talking about different
20 cases--an antibody positive that was a
21 carryover from the prior year.
22 So the clinical case that was

1 observed in January turned out not to be a
2 new infection but recognition of an older
3 infection. We haven't seen cases to support
4 testing--you know, one of the questions that
5 we ask as an industry was do we even need to
6 test, as they do in Hema-Quebec, they suspend
7 testing during the non-mosquito season. I
8 mean, you need mosquitoes to transmit, and in
9 areas where there are no mosquitoes, perhaps
10 we don't need to test.
11 But we have agreed with travel,
12 and because not all of the United States does
13 lose mosquitoes, but we, as a country, will
14 continue to do minipool NAT, year round. But
15 I can't explain the disconnect other than
16 delayed reporting for those clinical cases,
17 because we don't see it in blood donors.
18 DR. KUEHNERT: I just wanted to
19 make a comment about the false positives for
20 ID-NAT. It looked like, from the chart, I
21 mean, certainly, when you have a low S to CO,
22 I mean, it indicates that, you know, it's

1 probably a false positive, but not for sure,
2 and even when you get up to the higher
3 numbers for ID-NAT, you could have an S to CO
4 over thirty and it could be a false positive.
5 So it seems like it's really hard
6 to figure it out, and it particularly has
7 implications if we're talking about moving
8 towards ID-NAT more often, and also for organ
9 and tissue testing, because they can't do as
10 much, you know, resolution, can't follow up
11 with the donors.
12 So it makes it more difficult. I
13 just wondered if there's any more research,
14 along the lines of what was asked before,
15 about what produces a false positive,
16 particularly in the setting of ID-NAT and
17 trying to further discern a false positive?
18 DR. STRAMER: Regardless of how
19 complex West Nile is, or complex NAT is, the
20 answer to false positives is extremely
21 simple.
22 It's contamination. So for sites

1 who don't cram through 5000 tests a day, who
2 have technologists who are highly proficient,
3 and in many of the facilities, who just
4 perform organ and tissue testing, I think,
5 you know, those are probably smaller numbers
6 and plagued with less proficiency than the
7 giant blood centers who do this as their
8 "apple pie," so to speak.
9 And also I will comment that doing
10 organ and tissue, they do them individually,
11 so the chances of having a false positive do
12 increase. And then I'll also comment that
13 not all lots are created equal, and there's
14 some magic, sometimes, into driving the
15 enzyme or probe into solution, and if there
16 is any precipitate left in some of these
17 solutions, those lots become very highly
18 prone to--I don't want to say some type of
19 biological false positive, not related to the
20 sample, but related to the dynamics of the
21 test. So it's a tricky business, and the
22 organ and tissue folks do have a formidable

1 challenge.

2 DR. SIEGAL: Dr. Rios.

3 DR. RIOS: Sue, I hate to bring
4 the ten samples again, but the ten specimen
5 that did not repeat NAT, what is clearest to
6 me--and I don't mean to talk about tissue
7 because we are discussing blood--but how
8 would you know that the false positive rates
9 are so high, if you don't have follow-up of a
10 100 percent to see sort of conversion.

11 And I understand, and I know you
12 can't do it, but when we claim claim that
13 it's false positive, you have to have the
14 basis of at least having a follow-up. Lack
15 of follow-up does not indicate false
16 positivity.

17 So if you have a donor that was
18 reactive and did not repeat and didn't come
19 for follow-up, they should not be regarded as
20 false positive.

21 DR. STRAMER: Well, as I
22 mentioned, our donor letters don't

1 necessarily tell them, you know, we give them
2 all possibilities, we do say you are likely
3 false positive, because the data do support
4 that they are likely false positives.
5 And the 540 carried on into the
6 additional analysis were followed, and shown
7 by two types of NAT, and antibody, that they
8 were false positive.
9 I know those ten will occur, but
10 we have to also recognize, even if we require
11 follow-up, not all donors are going to
12 participate in follow-up.
13 It happens to be amazing. We
14 looked at all of our--for purpose of writing
15 a reentry chapter, we looked at all of our
16 follow-up for donors and reentry numbers, and
17 the marker that we have the highest success
18 rate for on donor follow-up happens to be
19 West Nile.
20 Each year, it's about 75 percent,
21 the donors, without really twisting their arm
22 or hitting them over the head with a bat,

1 that you have to come in for follow-up, they
2 do participate, and, you know, why isn't that
3 high for HIV or HCV? And the only thing that
4 we can surmise, which is off the topic, is
5 that this doesn't have a behavioral stigma.
6 I mean, there's nothing wrong with
7 getting socially--it's socially acceptable to
8 be bitten by a mosquito, even though some of
9 our HIV-positive donors tell us that's how
10 they were infected.
11 But in any event, we're not going
12 to get all donors to participate in follow-
13 up.
14 DR. RIOS: I do appreciate and
15 understand your point and I am not
16 questioning about the safety of public
17 health, that you have to cover everything,
18 but the scientific basis by which you
19 nominate them false positive, that I'm
20 questioning.
21 So maybe it's more appropriate to
22 say that it's inconclusive than call them

1 false positive, if you lack follow-up.
2 DR. STRAMER: Well, our letters
3 actually do use "inconclusive," they use kind
4 of innocuous words such as those.
5 DR. RIOS: Thank you.
6 DR. SIEGAL: Dr. Schreiber.
7 DR. SCHREIBER: Sue, I understand,
8 I think I understood that part of the trigger
9 system is dependent on the individual testing
10 labs putting their information into a third
11 party Web site, AABB Web site, and this then
12 can be used to decide whether a trigger takes
13 place, for example, if it's by zip code or
14 geographic area.
15 It seems to me that when you have
16 a big system like yours, where you're
17 controlling the labs, that's a pretty good
18 system. But when you're dependent on others
19 to have to put something in, without any
20 mandatory requirement, that seems to me to be
21 a little bit of a weak link in the system.
22 Is there anything being done now

1 to try to work towards that? I know you said
2 that the communication link was a problem.
3 DR. STRAMER: It's not a problem;
4 we've just never encouraged it before. I
5 mean, we have encouraged--Barbie Whitaker's
6 microphone, she'll address for AABB--but
7 we've never--none of this is mandatory, but I
8 think we all want to do the right thing. I
9 mean, we all want to protect the safety of
10 our recipients, and the only way for us to be
11 able to--well, one way for us to be able to
12 identify what's happening in the United
13 States is for us to have a very active Web
14 site for which all of these cases are
15 reported.
16 Within the Red Cross, I'm going to
17 do something in addition to the Web site, as
18 you mentioned George, but I have the ability
19 to do that. I can send out to every
20 institution that's also on the AABB Web site.
21 I can send them out a weekly update. I'm
22 going to include them in our con calls when

1 we trigger, so that there are no secrets, to
2 make this completely transparent.
3 But, you know, yes, it is
4 voluntary.
5 DR. SIEGAL: In the back.
6 DR. SCHRIEBER: It's voluntary but
7 many centers are making it SOP, and, you
8 know, that's as close to mandatory at my
9 center as you can get, is it's an SOP that
10 says within x number of hours of a
11 presumptive positive, it's going to be on the
12 AABB Web site. I'm hoping that most places
13 are doing it now.
14 DR. STRAMER: Yes. We have it in,
15 yes, the SOP as well.
16 DR. WHITTAKER: Just to add to
17 that, Barbie Whittaker, AABB, last year it
18 was not required and we had 430 PVDs
19 confirmed positive, that were entered into
20 the Web site, which is more than were
21 reported to the CDC, and the average number
22 of days--and this wasn't required--it was ten

1 days from date of collection to date of entry
2 into our Web site.
3 So I think it speaks pretty well
4 for the compliance, when it wasn't even a
5 required system.
6 DR. STRAMER: And the association
7 bulletin now--well, it requires within 24
8 hours of reaching the trigger, that you
9 actually initiate testing. But I think we
10 used pretty strong language in the
11 association bulletin as well, to which the
12 speed you enter into the Web site.
13 DR. SIEGAL: Dr. Kleinman.
14 DR. WHITTAKER: And we can send
15 our reminders too, to the members, to do
16 that.
17 DR. KLEINMAN: I just wanted to
18 add one point on ID testing, to kind of
19 address the question that Dr. Di Bisceglie
20 had asked before about infectivity. So I
21 think Sue mentioned this but just to
22 reiterate it. Number one, the people that we

1 pick up by ID-NAT, when we do the
2 quantitative testing, usually have less than
3 a 100 copies per mL, which is the limit of
4 the quantitative assay to detect.
5 And then, secondly, if you
6 actually look at transmissions from ID-NAT
7 positive units, you can have two kinds of ID-
8 NAT positive units. You can have the ID-NAT
9 positive unit at the very beginning of
10 infection, where there's no antibody, and
11 then the person goes through peaks of
12 viremia, starts to lose their antibody,
13 starts to lose their virus, and antibody
14 comes up at that point in time.
15 And so far, we don't have any
16 examples of transmission from a unit, that
17 I'm aware of, that was both viremic at low
18 levels, only detectible by ID-NAT, in
19 association with transmission, which kind of
20 mimics Hepatitis A situation, as an example.
21 And so most of the units that we
22 identify by ID-NAT are units that have

1 antibody. So the additional value we get
2 from ID-NAT, in terms of preventing
3 transmissions, may not be 22 percent. The
4 additional yield we get is 22 percent but not
5 all of those units may be infectious. It may
6 only be that initial window.
7 If it's correct, that the initial
8 window is the important period of time, which
9 we all believe, then obviously it's important
10 to trigger very quickly because once the
11 epidemic is spreading through the community,
12 that's when you're going to have people
13 acquiring infection, presumably in an initial
14 wave, and if you wait too long to trigger, if
15 you wait a couple of weeks to trigger, when
16 the mosquitoes are no longer perhaps
17 transmitting the disease, you'll still pick
18 up a lot of people who are ID-NAT positive
19 but they're probably not the most infectious
20 people.
21 So just a couple of additional
22 comments about how to think about ID-NAT.

1 DR. SIEGAL: Dr. Kuehnert.
2 DR. KUEHNERT: I wasn't going to
3 bring this up but since it's been brought up
4 again, I just want to urge some caution about
5 stating that transmission doesn't happen
6 with--
7 DR. KLEINMAN: I said we haven't
8 detected it, Matt. I didn't say it didn't
9 happen.
10 DR. KUEHNERT: Okay. But the
11 denominator is very small. I mean, we're
12 talking about less than thirty, because, for
13 instance, in the 2006 cases, we didn't even
14 have a sample to test for antibody, to look
15 back. So that doesn't even add to the data,
16 and we sort of have to be cautious about
17 that.
18 And the other point is that in the
19 organ transmission case, that was last
20 reported and given, that's organ
21 transmission, the donor was antibody positive
22 and NAT negative.

1 So it does happen in the organ
2 transplant world, although I agree that's
3 very different from blood, but we just have
4 to--but I just wanted to give that caveat.
5 But I agree with what you said.
6 DR. KLEINMAN: I think that's
7 true, that it's not an absolute statement,
8 but I think we should regard units in the
9 initial period as perhaps more infectious or
10 more likely to be infectious than units, once
11 a person's developed antibody. It's not an
12 "all or none" phenomenon, probably.
13 DR. KUEHNERT: Sure.
14 DR. RIOS: I appreciate the
15 discussion and I respectfully disagree with
16 you, Steve. Of course. Why would it be fun?
17 But there are two things that happen here.
18 One is that the absence of
19 evidence is not evidence of absence, first of
20 all. And we do not definitely test every
21 single recipient during the period of West
22 Nile season.

1 Second, we have published that in
2 primary human T-cell, monocyte culture,
3 antibody does not make any difference in the
4 infectivity. Second, there is the
5 information about the organ and donors, and
6 then we are publishing a paper now in
7 Clinical Infectious Diseases, where we show,
8 in collaboration with Dr. Stramer, that red
9 cell attach to--West Nile attach to red cell
10 and it can be as high as one log higher than
11 in the plasma. I would like to remind you
12 that we use plasma to test. So if the red
13 cell compartment is saturated, you cannot say
14 that because of the absence of the low viral
15 load in the plasma, wouldn't be infectious in
16 the red cell.
17 In the presence of antibody, I
18 would like to remind you that some flavivirus
19 has AD, that it's enhancement of infectivity
20 by the presence of antibody. Second of all,
21 neutralizing antibodies, performed in a
22 completely official system, using kidney cell

1 from green monkey, and, you know, cultivated
2 in lab, so it's not a natural situation. I
3 would like to caution you to evaluate this as
4 lack of absence, or the evidence be evidence
5 of absence. Another point is if
6 you are testing low viral load in plasma, in
7 pool, unlikely that you detect those ones,
8 that the red cell units may have high viral
9 load. So you may trigger much later, if you
10 have one rate, or one in a thousand, you may
11 have to drop this to one in five thousand, or
12 one in ten thousand. I don't know.
13 DR. DI BISCEGLIE: I have one more
14 discrepancy I'd like to explore, and that is
15 this issue of informing the other blood
16 centers in the region that a test is
17 positive, I think is very important, and I
18 guess I heard that at some centers, within
19 hours, a positive is reported, and then I
20 heard from somebody on the floor that the
21 mean time was ten days for this to be
22 reported on the Web site. Can you clarify

1 for me.
2 DR. STRAMER: That was last year,
3 when we just brought up the Web site. We
4 didn't talk about using the map or the Web
5 site as a tool for communication. That was
6 just a tool for reporting. So there was no
7 encouragement to rapidly report results,
8 which this year is very different, and the
9 AABB Web site is actually only one way for
10 labs to communicate.
11 DR. DI BISCEGLIE: I hear you but
12 what I'm getting at here is whether there is
13 a need for the Agency to regulate the timing
14 as opposed to relying on voluntary reporting.
15 DR. STRAMER: Well, as Dr. Katz
16 also mentioned, if it's in our SOP, you're
17 required, by law, to follow our SOPs. So I
18 would argue that that's the same. But I
19 think what we need to do is review the
20 association bulletin and if we can tighten up
21 that language, we can certainly encourage
22 members to enter data within a given period

1 of time to speed up the process.
2 I think it's in everyone's
3 interest to do it quickly and I do believe
4 that blood centers understand that, at least
5 the ones that I've talked to, and since the
6 association bulletin has come out, I've had
7 lots of calls and lots of e-mails.
8 DR. SIEGAL: Is there any more
9 discussion? If not, I believe we can
10 adjourn. Any objection? Have a nice
11 weekend. You had a question or a comment?
12 DR. NAKHASI: That all of you had
13 a chance to comment because, you know, we ask
14 specifically, when we talked about on slides,
15 Maria talked about we are considering this,
16 we are considering that, that you didn't have
17 any other discussion on that, because I know
18 you focused mostly on the ID-NAT trigger, but
19 did you have any comments on the positive
20 predictive value of the, you know, false
21 positives and other things?
22 So I just wanted to make sure,

1 because I think, you know, sometimes, because
2 we didn't ask the questions, I just wanted to
3 make sure that there are no comments.
4 DR. SIEGAL: Anyone?
5 [No response]
6 DR. SIEGAL: All right. Thank you
7 all very much.
8 (Whereupon, at 3:04 p.m., the
9 meeting was adjourned)
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