children and their older siblings, and I believe the earliest reports from those studies will be reported at ICAAC this year, if not at SPR. I don't remember.

I think you're familiar with a very extensive set of studies done not in this country, but Israel by Ron Dagan, and without going into those, I think what's striking in the Dagan studies, which were in a day care center setting, is that the nine-valent vaccine reduced carriage by 40 to 50 percent in the recipients of vaccine versus control, reduced antibiotic resistant strain carriage significantly, and it also reduced carriage by vaccine types and by antibody resistant types, in the siblings at home of the children who were immunized as composed to the day care attendees who got the control vaccine.

So there are clearly effects on carriage and carriage of antibiotic strains at least in that very controlled setting in Israel.

ACTING CHAIRMAN DAUM: And taking people out of order who can speak to this very issue, Dr. Kim.

DR. KIM: I think there was a somewhat interesting article published in Nature recently implying that in their case they were talking about vancomycin, but antibody resistant Strep. pneumoniae

had greater capability of transformation than with acquiring other antibody resistance, as well as transmission with potentially other capsular genes.

So I think this issue about antibody resistance would be potentially important not only before the licensure, but also post marketing surveillance.

ACTING CHAIRMAN DAUM: Thank you, Dr. Kim.

As a clarification, those isolates weren't resistant to vancomycin. They were tolerant. That is to say they were not killed, but they were not resistant.

Dr. Katz, is your question about this issue? Would you go ahead, please.

DR. KATZ: It wasn't a question. It was just a comment in that I think what we're hearing is the problem of the heterogeneity of different populations. What I didn't hear mentioned, I believe were Dr. Keith Klugman's studies from South Africa, which were in some ways quite different from those in Israel, and I think it just highlights the idea that you can't generalize from one population to another as to what the effects of vaccine are going to be depending on what the ambient organisms are and what is the situation of the population whom you're

studying.

So that I think if you're going to study what happens in the United States, it may be different from Montana to Massachusetts, but at least it makes it implicit, I think that any recommendations you're going to make for this country are going to depend on what the data are for the United States and not a study done elsewhere.

ACTING CHAIRMAN DAUM: Well, let me throw out an idea that I think I'm hearing weave through people's comments and see if people like it or don't, but I'm getting a sense that you just sort of can't go off and study pneumococcal disease anyplace you like and believe that we can take the messages home, if you will, and bring them back to the U.S.

And so if an alternate site is contemplated for study, we've got to know something about the baseline there. What's the epidemiology? What's the carriage? What's the responses to vaccine? How does it compare with what we have in this country?

And then one can undertake study of choice, and then we can interpret the data based on those baselines.

I mean, I think that's what people are saying in about ten different ways. Does anybody want

to comment on that or does anyone agree with it or disagree with it?

Dr. Broome.

DR. BROOME: I mean, I'd never deny that there's a lot of variability and idiosyncracies, but I also think for the serotypes producing invasive disease, there's actually been remarkable consistency over time and geography. There's exceptions, but you know, big picture, I don't want us to be so nihilist that we ignore what I think could be valuable data on IPD protection in other countries.

I do think the carriage area is enormously complex, and I look forward to further understanding.

ACTING CHAIRMAN DAUM: Yeah, I accept that as a -- that's a clarification, I think, in one area where that might not be quite so true, but anybody else want to comment on this? Dr. Griffin, Dr. Butler?

DR. GRIFFIN: Well, yeah, he's going to be able to comment more knowledgeably. I was just going to ask if the same thing was true about otitis media as it is for invasive disease when it comes to the serotypes most likely to be causing disease. Is that also -- we don't have much of a database.

DR. BUTLER: I don't know. My comment

was, you know, I think the distinction between carriage and invasive disease is very important, and to sneak ahead and look at some of the other questions coming up, we need to keep in mind that same difference probably applies to otitis media versus invasive disease.

And if any two of these three are similar, it's probably carriage and otitis media.

DR. BROOME: But you have to be real careful about how certain you are of the causative isolate, and you know, otitis has its own set of complexity.

ACTING CHAIRMAN DAUM: Well, to come back to you, do you agree with the summary statement that I made, with the exception of invasive disease? I mean, I think we've got to try and struggle with this because it's going to come up over and over again.

Does a country that is going to have a study undertaken and it needs some definition of what goes on there before the study is undertaken.

Anyone want to comment on that? Dr. Decker?

DR. DECKER: You know, in evaluating our alternative measures of implied efficacy, other than doing an actual efficacy trial, the considerations

that have been given are being given to antibody levels or let me phrase more generally.

Immune response, however we decide that ought to be measured, or various thought relevant or clearly relevant clinical outcomes, like occurrence of otitis, carriage with pneumococci and so on, and those clinical outcomes are attractive to use either as primary or secondary endpoints because they're relevant clinical outcomes.

But I think there's a lot of danger in them also, and they're at least as dangerous as any serologic criteria. For example, as we've just heard, the characteristics of colonization and the impact of the vaccine on colonization differ markedly from population to population in such a way that you can't presume -- I mean, the same vaccine basically is shown to be highly effective in preventing colonization in one population and marginally effective in another. So a candidate vaccine might look highly effective or marginally effective when, in fact, it's no different at all from Prevnar based on which population you did this in if colonization were an endpoint. So that's a dangerous endpoint.

If otitis is the endpoint, I've got a number of concerns. One is that, again, the

mechanisms involved in otitis are not the mechanisms involved in -- the same as in invasive disease.

The FDA raised the question or whether or how the committee would respond to a vaccine that was brought in simply for licensure on the indication of prevention of otitis, and that's a very interesting question, but let's set that aside and suppose the question is: how do we respond when otitis prevention data are being used to support a claim of efficacy against invasive disease?

Well, I've got a number of concerns with that because I suspect, for example, that prevention -- this is based on largely extrapolation from Hib, but I suspect the prevention of otitis may be more dependent on GMT, whereas prevention of bacterial disease or bacteremic disease depends upon a minimum protective level; that there may be different mechanisms.

And I suspect it's possible that a vaccine that's effective against otitis might be more or less effective than Prevnar against invasive disease.

So extrapolating from otitis to invasive disease may be at least as shaky as extrapolating from any serologic criteria. I mention that just to give caution because I think there's a natural tendency to

favor the clinical criteria, and they may not, indeed, be any more reliable.

ACTING CHAIRMAN DAUM: Okay. We have Dr. Goldberg, Dr. Insel, and Dr. Giebink lined up for comment, and we're starting to get near a time when we will start focusing on these questions.

DR. GOLDBERG: I want to bring up something I think we should talk about, and I don't know if it's reasonable in this arena, but in many instances when you have an endpoint that's very rare, but very serious, you have other endpoints, clinical endpoints, that also can be assessed in the same population.

And it seems to me that one possible approach to this is to do in quotes clinical efficacy trials using a combined endpoint, which is really the occurrence of a series of events that could be prevented by this vaccine, such as the invasive disease such as otitis media.

And you can prioritize them in order of severity so that you would have the worst first, if you will, I mean, the details to be thought about, but something starting to think along those lines though opens up an arena where you would be doing a clinical efficacy trial on a population, on a sample size that

was considerably smaller than the one that you'd need for the invasive studies, quite larger than the ones that have been proposed for the immunogenicity studies, and begin to give you enough data that would accumulate on safety and ways of assessing the immunogenicity in relation to these various endpoints.

And I think I'd like some discussion of that. If it's off the wall, I accept that, but I know that in other arenas it is not.

ACTING CHAIRMAN DAUM: Anybody care to respond to Dr. Goldberg's comment?

(No response.)

ACTING CHAIRMAN DAUM: Got no takers right now.

Dr. Insel.

DR. INSEL: With respect to question one and two, one theme that I've heard this morning was the importance of measuring functional antibody, and yet I'm troubled by the utility of the current opsonophagocytic assays and whether or not they're going to prove useful in this regard.

There's an article this month in the Journal of Clinical and Diagnostic Laboratory Immunology by Helena Kayhty where she and colleagues have compared four different opsonophagocytic assays

that have been developed worldwide, and one theme that comes through in the article is the lack of sensitivity of those assays, especially as one gets into the concentrations of less than one microgram per mL.

And yet when it comes to ELISA assays, I'm hearing that we're willing to use ELISA values of, let's just say for the sake of argument here, say, less than 0.5 micrograms per mL, and I'm wondering if somebody from this community can just at least begin to address how are we going to use opsonophagocytic assays as a functional assay if we don't have the requisite sensitivity today or even in the short term. I'm not sure where the field is going, if that could be addressed.

ACTING CHAIRMAN DAUM: I think we should ask Dr. Frasch to respond to that first, and then we can have other responses, if you would.

DR. FRASCH: Well, I think one response to that is just for the sake of argument, 0.5 microgram per mL, somewhere in the vicinity of 90 percent of recipients have greater than that following post dose three. So what has been done in the past is take those recipients who have made antibodies in excess of one microgram and then find out if those particular

individuals' antibodies are functional.

So that's the approach that's been followed, and I'm not sure that you can say that if you have .2 microgram of antibody that antibody is going to be of lower quality than an individual who makes two micrograms.

DR. INSEL: Again, I'm not sure what the basis of that statement is either. I mean, I'm concerned that, you know, we start talking about levels of .2 as being the criteria based on ELISA, and now you say, well, secondly we have to measure functional antibodies, and yet it's only a subset of that group in which we can measure functional antibodies, and presumably those individuals who are making higher antibody titers may be making antibodies with higher affinity and may have more functional activity.

And so I'm not sure one can extrapolate just from the select group of individuals who make one to ten micrograms per mL as far as what's going on with the whole group, and I think that's going to have to be addressed if this is going to be used as a criteria.

ACTING CHAIRMAN DAUM: Dr. Giebink had his hand up, and then Dr. Kohl. We're going to stay on

this issue for a bit and try to explore it.

DR. GIEBINK: No, I just wanted to weigh in on this issue myself.

ACTING CHAIRMAN DAUM: You're next to speak anyway.

DR. GIEBINK: My understanding from the report out of the workshop was not that avidity assays or opsonophagocytic assays would be used in the same quantitative way that ELISA results are used, but rather that avidity assays and opsonophagocytic results would be used to characterize the response that a vaccine elicited in an early phase experience with that vaccine, and that if it had the same characteristics as the Prevnar response, you'd move along, but you'd do so with ELISA.

And I guess I just want clarification, Carl, if that is the gist of what the workshop discussion was.

DR. FRASCH: Yes, yes, because what you're really trying to show is is the vaccine capable of inducing functional antibodies, and to do that you don't have to look at antibodies in every single individual that were immunized because what we're concerned about is does the chemistries, the chemical modifications, required to make the polysaccharide

able to chemically link to the protein, do these chemical modifications have an effect on the ability of the resulting conjugate to induce functional antibodies?

So that's partly where we're coming from from the standpoint of looking for the ability of the vaccine to induce functional antibodies.

ACTING CHAIRMAN DAUM: Dr. Falk, then Dr. Kohl.

DR. FALK: I just wanted to speak directly to Dr. Giebink's question.

I think you encapsulated the sense of the workshop very well in that the end result would be an evaluation by ELISA for the pivotal study, but that during the course of the product development and clinical evaluation, there would be an evaluation of the ability of the ELISA to correlate with opsonophagocytic and avidity endpoints as well, but not necessarily -- the workshop did not get into in my mind the specifics about how that was to really happen, just that it could be done in a subset during the pivotal study or prior to the pivotal study.

ACTING CHAIRMAN DAUM: Okay. More about this -- sorry, Claire. What did you want to say?

DR. BROOME: I just wanted to comment on

this point.

ACTING CHAIRMAN DAUM: Would you, please?

DR. BROOME: I mean, it seems to me there's actually two ways in which the functional assay could be helpful. One is what I think Carl is referring to, which is the generic question: does a serotype for which we don't have efficacy data elicit functional antibody, you know, at all, in which case the higher titers presumably are relevant?

But I think the other issue that Dick and I was sort of interested in was could the functional assays help up with this issue of what is a meaningful threshold value, in which case you really need to focus on the ELISA values that are in the lower range.

And I'd just still be very curious as to whether there is, you know, any progress in both reliability and sensitivity of assays in that range or whether it's an impossibility. I just don't know enough about the mechanics of the assays.

ACTING CHAIRMAN DAUM: Yeah, I think this is an important issue to ask people here to speak to if they have knowledge about it because we're groping with this functional assay business, and it really looks like the higher titer sera are the easier ones to measure and that we've seen the most data about,

but they may also be the sera with the most functional antibodies.

So what do we know about low ELISA titer sera and function? Dr. Kim, what do you know?

DR. KIM: I guess I also want to, you know, raise one more issue related to that. Again, I want to raise this issue to Carl. He's, you know, performing a functional assay, such as opsonophagocytic assays. I know there are probably ten, 20 different ways you can set up the opsonophagocytic assays so that, you know, the question is, again, going back to some of the issues that Dick Insel raised about sensitivity: are you able to sort of set up the assay in a way that you will be able to measure functional activity of those sera regardless of concentration of antibody measured by binding assays to elicit functional activity?

DR. FRASCH: I would like to preface that in that the in vitro opsonic assay in itself is very different than in vivo. So it's a very artificial set-up right away.

Now you're asking us to twink the artificial assay such that it becomes sensitive enough to now measure antibodies at our proposed threshold value.

I'm not sure we're going to gain anything by making it maybe more artificial.

ACTING CHAIRMAN DAUM: Before I call on anybody else, is there anyone here who has information about this issue that's been nagging us, or is this the state of the art right now?

State of the art, Dr. Giebink nodding his head as an expert pneumococcal guy.

(Laughter.)

ACTING CHAIRMAN DAUM: All right. Dr. Kohl first, then Dr. Decker. We have some uncertainty identified.

DR. KOHL: I'm still on this same question, and I'm coming from it sitting on this side of the table as a beleaguered hireling of the FDA, and I'm looking down the road having a company come to us. We're basically talking about one, and I think we've accepted the first part of that one that we're probably going to accept noninferiority immune response, and we're talking about the second thing now, which is --

ACTING CHAIRMAN DAUM: I would ask you not to assume that.

DR. KOHL: Okay.

ACTING CHAIRMAN DAUM: For your comment.

DR. KOHL: Well, that's where I am.

ACTING CHAIRMAN DAUM: I don't think I've heard a clear consensus on that at all.

(Laughter.)

DR. KOHL: Well, as I'm sitting here, I'm thinking about a company that comes to us and says, "Well, here is our cutoff level, and we've made all of the whatever we decide, the hoop that you have to jump through for that, and now here's our opsonophagocytic level."

And what do we on this side of the table need to see? Do we need to see that 80 percent of the high titer serum achieved a certain level of the OPK? I'm trying to figure out how that's going to help us, and I'm hearing the very vague comments about, well, it will be used in early studies to show that the antigen is capable of eliciting an opsonophagocytic response.

I don't know what that means. Eliciting it in 100 percent of people or eliciting it in high titer people or eliciting it in two month old children?

And we're being led to think that the opsonophagocytic assay is somehow close to the human situation because it seems to be correlated with

animal models, but what about with polys -- I presume we're talking about polymorphonuclear leukocytes as the prime actor here -- what about polymorphonuclear leukocytes in a six week old or in a three month old where the action is, where those pneumococci are?

So it's very complicated, as Dr. Insel was, I think, implying, and I think as Dr. Decker also said.

ACTING CHAIRMAN DAUM: Thank you, Steve.

Dr. Decker. Dr. Hall next.

DR. DECKER: There's current discussion. I think it may be best addressed by coming back to what Dr. Goldberg said because I think, again, on a practical level that's likely to be the way we end up heading.

If, and I agree with Steve on this notwithstanding my deep respect for the Chair, I think we're probably headed towards taking a -- eventually identifying some immunologic pathway to licensure. If we do that, we're going to want assurance that that in vitro measure has in vivo meaning, and that assurance may come at least in part through identifying some specific other immunologic test, such as opsonophagocytic antibodies, or it may come from some of the clinical endpoints that I cautioned against

using as determinative earlier, but which I think clearly we might want to use as supportive.

And that brings us directly to what Dr. Goldberg was saying. For example, I can contemplate a checklist where, yes, we've achieved antibodies measured by ELISA in the total immunized population, study population, that meet these criteria with comparison of Prevnar for the strains contained in Prevnar.

And in addition, we've shown that in an appropriately selected subset in whom it can be done, we've demonstrated activity of these antibodies, and in addition, we've shown an impact on some clinical endpoint which is reasonably comparable to what you achieve in that endpoint with Prevnar, and therefore, we have taken one from column A, one from column B, and one from column C. Let's ship our order. It's ready to go.

ACTING CHAIRMAN DAUM: Okay. I think we may as well swing into question one, but let's hear from Drs. Diaz and Goldberg, and, Dr. Hall, you had your hand up first. I lost.

Let's go with Dr. Hall, DR. Diaz, Dr. Goldberg, and then we're going to go right into question one.

DR. HALL: Still on the same question obviously, coming back to what Dr. Broome said earlier, which I think is really important, is how much variability between the functional assays and ELISA exists in terms of serotype, and I'm wondering if anybody has more data or if Scott perhaps has it at least in the animal model.

And secondly, since we appear to know that the pre-titer does affect the ELISA titer, is that also going to affect the functional assay?

ACTING CHAIRMAN DAUM: Anyone want to address that question? I'm sure I'm missing some information here.

DR. GIEBINK: Yeah, I got put on the spot here.

ACTING CHAIRMAN DAUM: All right. Who put you?

DR. GIEBINK: I think I need to say on the table for all to know that the correlation between opsonophagocytic titers and ELISA titers is in some cases good and in many cases not so good.

DR. HALL: By serotype.

DR. GIEBINK: By serotype, and in no case is it great. So I'm not going to put numbers, Rs on those, but really there's quite a scatter. So I have

a lot of concern about using opsonophagocytic titer as a surrogate for protection because I feel better about ELISA titers, IgG titers and their relationship to protection, but neither is perfect.

ACTING CHAIRMAN DAUM: So are you saying that the focus, and hearing the footprints of issue one coming, the focus ought to be on measuring ELISA because like it or not, that's the best we've got, and then some kind of functional assay, I presume we would want to work in there, to make sure that what we're measuring by ELISA works?

DR. GIEBINK: Yes. That's what I -- I think that's what the workshop concluded, and I would agree.

ACTING CHAIRMAN DAUM: But then we're getting squishy as to what that something should be and how it should be done is what I'm hearing.

DR. GIEBINK: Okay.

ACTING CHAIRMAN DAUM: Right?

DR. GIEBINK: Yes. That's true. I think we may have to be comfortable with the squishiness for right now.

ACTING CHAIRMAN DAUM: Dr. Frasch, on this issue?

DR. FRASCH: Yes, but I don't think -- if

you read question one, I don't think it infers like you're saying, one assay, one measure, one immune parameter.

ACTING CHAIRMAN DAUM: Well, there's a little parentheses at the end, but it certainly asks about it. You're the interpreter of the questions. I mean, is that not what you're asking?

PARTICIPANT: No, not really.

DR. GRUBER: I was just accused of having written this question, and you have no idea through how many revisions we went to arrive at this, but let me comment.

I think what is meant here really is what immunological parameter. I think we're thinking of perhaps being able to define today a primary parameter and then leave space for some secondary parameters that could be perhaps translated in secondary endpoints or something like that.

ACTING CHAIRMAN DAUM: It sounds like that's what you're going to get.

Dr. Diaz, please.

DR. DIAZ: I'm going to hold my comment or it will come up later.

ACTING CHAIRMAN DAUM: All right. Dr. Goldberg.

DR. GOLDBERG: Yeah, I just wanted to clarify something in what I said because, Dr. Decker, I mean, I think I agree with you, but to a point. I think that this, quote, clinical trial would also have the immunogenicity assays done. You would use those to bridge the secondary immunogenicity trials, but that would be the link.

And you would also be in that trial -- hopefully it would be sized so that you could at least for some of the endpoints or the combination of endpoints develop the relationships between the titers and the clinical endpoint.

So I wouldn't call the clinical, this thing, purely supportive. I would say that this would be in a sense -- it would have to be an agreement because it wouldn't be your standard clinical trial with all of the criteria tied up nicely, but in a sense, I would view that as, you know, one of two parts, and it would be a package of the immunogenicity trial with this that would determine your efficacy.

ACTING CHAIRMAN DAUM: Dr. Faggett, please.

DR. FAGGETT: Dr. Goldberg, just for clarification, so in effect you're saying the clinical trials would be available to validate pretty much some

of the other --

DR. GOLDBERG: But it would be a modification of the kind of efficacy trial that we talked about.

DR. FAGGETT: Yeah, I thought that's what you said, and my concern was that we're moving towards eliminating the availability of clinical trials, and to me I think that would be a mistake.

ACTING CHAIRMAN DAUM: I think we're trying to decide what their components should be.

Dr. Kohl and then Dr. Giebink.

DR. KOHL: I'm wondering as we move approaching question one if we can mandate a large post licensure trial, a bridge of immunology to licensure, and then a large post licensure trial, in particular focusing on rare adverse events and also breakthrough cases of pneumococcal disease, in particular, invasive pneumococcal disease, which may then give us a handle on serotype breakthroughs in particular, which will be unusual, but may be very telling.

ACTING CHAIRMAN DAUM: We are, of course, an advisory committee that mandates nothing, but we can certainly make the suggestion, and I know our colleagues are listening carefully to what we say.

Dr. Giebink.

DR. GIEBINK: Just a comment on the efficacy trial that Dr. Faggett mentioned. If I were acting from an ethical basis on the conduct of a clinical trial, because it's an equivalence or this scenario, I guess, called the noninferiority, but some of us think of equivalence trials; if this were an equivalence trial, I would require serologic evidence of equivalence before conducting the clinical trials.

So that, in fact, the first threshold in my mind is the serologic equivalence.

ACTING CHAIRMAN DAUM: Well, Scott, let me reframe your comment and make sure we're on the same page.

If we look at this item, this item basically asks about that, whether a noninferiority immune response, immune response, comparing a new vaccine with Prevnar are sufficient. So it really deals with what you're saying, doesn't it?

DR. GIEBINK: No. It's the issue of going on to clinical efficacy.

ACTING CHAIRMAN DAUM: To clinical, not this?

DR. GIEBINK: I was addressing this issue here.

ACTING CHAIRMAN DAUM: Okay. Dr. McInnes and then Dr. Griffin.

DR. McINNES: The concern with that approach is if you took the experience we had with hemophilus and you applied that to Hib OMP, you would have failed on a noninferiority basis --

DR. GIEBINK: But had equivalence, yeah.

DR. McINNES: -- but your efficacy data was spectacular. So you have a vaccine that works or has an immune response that is not in the traditional one you're comparing to, and you potentially kill a very important vaccine approach.

So I think the issue comes that if you have clear noninferiority on either of the serotypes, that's a win-win-win all around. The question comes if you don't have clear noninferiority in all of the serotypes, how much window do you give around that, and perhaps that's the first test, is the noninferiority, and if you don't pass by whatever the passing grade is, these other alternative approaches have to be open to look at, and the onus is then on to demonstrate efficacy or use some other supporting data to make the case for what might be taken into consideration for licensure.

ACTING CHAIRMAN DAUM: I think that's a

wonderful clarification for us. The language does use the word sufficient, and I take it from your comment, Pam, that you would say that it would be sufficient if it were noninferior.

DR. McINNES: Yes.

ACTING CHAIRMAN DAUM: And the corollary, of course, is that that would not close the door on further considerations. I think that's what I'm hearing.

Dr. Griffin, was it you that was next?

DR. GRIFFIN: Were you going to comment on that?

DR. DECKER: Well, very briefly. I agree entirely with Pam, and that's consistent with what I said originally. I think what we will need to end up with is multiple pathways to licensure.

For example, if we endorse a serologic pathway, there is always the efficacy trial pathway. We're not closing that door.

ACTING CHAIRMAN DAUM: So let's go to question one. Let's go to the big board.

Do you want to make a comment first? The last comment.

DR. GRIFFIN: Okay. The last comment. Because the only thing I wanted to say was solidify

the fact that if we go to an ELISA type of threshold, which I agree is much easier to quantitate, et cetera, as the serologic criteria that we're using, that I would agree with the comments that were made before. I guess I just wanted to reinforce it, that at some point prior to using the ELISA, you show that this particular kind of conjugate for each of these polysaccharides does induce functional antibody. I mean, this opsonophagocytic, you know, test sounds like a reasonable one, although not perfect, but that you would have to establish that, but you weren't only inducing ELISA reactive antibody.

ACTING CHAIRMAN DAUM: Okay. I'd like to start focusing specifically on this question now, and it has two distinct parts to it.

The first part is whether noninferiority -- comparing a new vaccine with Prevnar. So I'm going to presume -- FDA people, correct me -- that there couldn't be new serotypes in that vaccine for this question because then they couldn't be compared, and so if noninferiority, is it sufficient? Would it have to be done -- when you comment, would you please comment would it have to be done in the United States or could it be done, inferiority done, in South America, in Asia, in

Western Europe? Noninferiority done where?

And also when each person comments, we'll need to say something about what do you mean by noninferiority. First, what assay, primarily; second, what assay secondarily; and then, thirdly, what if not every serotype meets the bar?

I'm going to throw that in as an issue that I think would be worth commenting on as we go around.

Dr. Insel, I think we'll start with you if you wouldn't mind, and then we'll go up the table here and swing around.

DR. INSEL: And if I heard you, I think it would be sufficient if it was conducted in a comparable population, a U.S. population.

I think as far as immunological parameters, I view the ELISA is probably going to be your primary criteria, but I am concerned that we are going to set the threshold so low that we have to have some kind of functional assay, I believe, to go along with this, and I'm concerned that the functional assays as they exist do not have the requisite sensitivity and show serotype differences.

I am troubled with the 19F story because it's unclear to me. If I understand it correctly, 19F

does make pretty good antibody response both based on geometric mean concentration or titer, as well as a threshold type level, and yet on the invasive side there was, at least, one failure there which is obviously probably not meaningful, but on the otitis side of things, it is somewhat worrisome, and it makes me want to think that we do need to have some kind of functional equivalent if we are going to set this low threshold.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Wharton.

DR. WHARTON: I would concur with Dr. Insel's comments, though I also want to echo a point that I think you just made about that I'm not sure that I would conclude just because noninferiority criteria were not met that the vaccines were not equivalent.

Perhaps we'll get into that later, but I'm very concerned with a vaccine where we have a fair degree of uncertainty about threshold amounts. there are assay related issues. There are multiple assays being done, that when you include that very large number of analyses and comparisons, that the failure to meet noninferiority criteria for a couple of them

would eliminate a candidate vaccine, I think, could be a very unsettling discussion to be having in this room in a couple of years.

So I think that is an area that serves some additional exploration.

ACTING CHAIRMAN DAUM: Thank you very much.

So I take it both you and Dr. Insel believe that it would be sufficient.

DR. BROOME: I also think that it would be sufficient, but I think there's a number of additional points I'd like to make.

I mean, one is I think we do have to specify the precision of the assay at these low levels, assuming that the threshold is going to be under one, and so I want to know what the precision of the assay is under one, and I do think ELISA is very attractive for potential precision and ease of use for large numbers of samples, but if it's not measuring the right parameter, that really isn't that great.

I think on the whole it clearly does correlate, but I think when you're dealing with so many different serotypes and you have some evidence of, you know, if you take the otitis data different protection with different serotypes without that much

difference in ELISA, it makes me want to know a little more about something that would measure protection.

It also suggests to me that rather than sort of carving the narrowest threshold, we ought to have a sort of margin of error built in. You might determine that partly based on the precision of the assay. You also might just put in a margin of error.

I think that's also something you could -- which is sort of implied in this idea that rather than try to calibrate a threshold for each serotype, you pick, you know, a threshold that meets the highest serotype, which, you know, I think is what has been done by some folks, and it doesn't worry me that much to take that kind of an approach and use essentially that number for all serotypes, understanding that's making some assumptions.

The one thing I'm not comfortable with are these measures which combine the results across multiple serotypes. I think I've seen we've tried to do that over the years, and I really think that is a counterproductive endeavor which tends to sort of mask true serotype specific variability.

So those are just some thoughts, and you know, the issue, the one you tacked on of do we need to have noninferiority for all seven serotypes, you

know, I think that's a tough one. I'd prefer to have that. There's clearly some serotypes which are more prominent as causes of disease that would be priorities, but you know, I'd like to see if we couldn't do it for all seven.

ACTING CHAIRMAN DAUM: Dr. Butler.

Thank you. The first three speakers are just incredibly helpful, I think. So thank you. And let's see what else we can get from our group.

DR. BUTLER: Great. You've set me up, Bob. Thank you.

(Laughter.)

ACTING CHAIRMAN DAUM: Yeah, I'm sorry. If I don't say it for the fourth, they just didn't cut it.

DR. BUTLER: I think that the noninferiority of immune response trial is a reasonable approach for inferring efficacy against invasive disease, and I think I would also go as far as to say it's sufficient.

ACTING CHAIRMAN DAUM: Jay, can you speak right into the mic so we can all hear?

DR. BUTLER: That's somewhat considering also what the alternatives are and what are really logistically feasible to do, and I would qualify that

by making it clear that I'm talking about a head-to-head comparison between the vaccine under evaluation with at this point in time Prevnar.

The struggle that I think we're all having is what is the definition of noninferiority. Some of the definitions that have been tossed around included some triple negatives. I find I'm having to pull out a piece of paper to keep track of just what it is we're implying.

But the question of what to do when there's, say, a single serotype that falls short, I think, is important. An example might be serotype 4. At least in the trial in Northern California that was a very unusual serotype, and it's not one of the leading serotypes in that age group in the U.S.

Does a vaccine then not go to licensure because of that?

The other issue is how to evaluate to immune response, and I think the attractiveness of the ELISA is standardization, but I think functional assays, such as the OBK and perhaps also avidity assays can provide very important complementary data, and I bring that up because that may be complementary data that would be useful in terms of sorting out what to do with the individual serotype or small number of

serotypes that fall short by ELISA.

I cannot even begin to imagine how to state that quantitatively, but just as a general concept, I think that complementary data may help sort out those questions, and I think that's going to really happen with expanded valency vaccines and the fact that we're dealing with seven individual immune responses.

There's going to be differences, if nothing else, due to chance.

ACTING CHAIRMAN DAUM: Thank you.

That was four very helpful --

(Laughter.)

ACTING CHAIRMAN DAUM: I can't keep doing it though.

Dr. Hall.

DR. HALL: Why not?

I can just say that I agree with everything that's been said in general, but I guess what I'd like to bring up again is, first of all, what of course is going to be sufficient is a question yet, but if you have populations that are comparable, which I think is the basis that everybody has said to utilize this, that means to me stepping back a minute and saying what are the criteria to determine that

these populations are comparable, particularly if we're doing it in another country, and I don't think that we've really addressed that issue.

Is it the distribution of serotypes? Is it their immunogenicity on a given serotype?

I mean, there are so many different aspects so that I think those would have to be set up first, and then I would think that obviously the immunologic parameter or the major assay would be potentially ELISA, and that as Jay brings out, that there will be some that are going to fall short.

So how are you going to judge those? And in those instances, maybe it does require a combined or weighted assays of all the assays, and that again then brings up the conundrum of trying to decide how do you weight this.

But I think all of those things need to be at least set up to some degree as to what our criteria are.

ACTING CHAIRMAN DAUM: Thank you, Dr. Hall.

You're next.

DR. EMERSON: I'm in the position of being allowed to both introduce the probably greatest heterogeneity of opinion and perhaps the heterogeneity

of quality of opinion.

I guess the main thing I have to address is the question of time. I mean, I think clearly eventually you have to go to the immunologic response, and my major question is: are we there yet?

And I guess I don't think we are. I haven't heard any evidence. You know, I guess I've heard it go both ways as to whether this should be necessary or sufficient. The idea of saying if you don't have the immunologic response, should we drop it like a live grenade or should we then go on to efficacy treatments? And quite differing opinions there.

And I guess I also think there are some numbers that I look at in these preliminary things that don't look that unattainable. Thirty-eight thousand people were used in the Kaiser study. There's quite a number of these sample size formulas that come up in the 38,000 range or better, particularly as you start considering that the otitis media endpoint can contribute such information.

And so I would be looking more at what I think you put as, you know, the one from column A and column B and column C approach, as the idea of saying we'd like some immunologic response, and that in

combination with some more protective endpoints on the secondary ideas of otitis media would be preferable to at this stage going with purely an immunologic response to declare noninferiority.

ACTING CHAIRMAN DAUM: You know, I thank you for your comments. You've touched on many issues with them.

But to come back to this very item, do you think that noninferiority is sufficient for inferring efficacy?

DR. EMERSON: No, no.

ACTING CHAIRMAN DAUM: Good. Thank you.

Dr. McInnes, please.

DR. McINNES: I think we should remember the spectacular efficacy of Prevnar, and we should remember, I think, the considerable body of data that supports that antibody is protective, and I think I have no problem in supporting the use of noninferiority immunogenicity studies, but the bar is set. It's out there. It's a licensed product, and that's the guy against whom you have to get measured.

And so if noninferiority can be demonstrated by immune response, and I think there's a lot of work being done on ELISA and there has been a lot of work done on the functional assay. It's not

everybody's favorite functional assay, and I think there's room for a lot more work in this area, but I think pragmatically the ELISA is working for us, and I think we should continue to try to refine the opsonophagal (phonetic) functional assay and the correlation between these two, but I am confident that these are meaningful at this point, and I have no problem supporting this approach for noninferiority of all the serotypes.

ACTING CHAIRMAN DAUM: Dr. Decker, you may choose to believe you've spoken to this already.

DR. DECKER: You know me better than that.

ACTING CHAIRMAN DAUM: I was actually going to say that, and I said, "Bob, catty. Just don't do it."

(Laughter.)

DR. DECKER: My answer to question one is yes. More specifically though, only if the question is broad enough to say that not an inferiority demonstration requires at least a little bit more than demonstrating the statistical noninferiority of the ELISAs because of the concern. Although we've got substantial evidence, as Pamela said, that antibody is the key thing, still we want to know the antibody that is being generated is functional.

Once we know that it's functional, then I think we can assume that the demonstration of numerical noninferiority is adequate.

I disagree a little bit with Dr. Emerson. I didn't mean to imply earlier that a candidate vaccine would need to demonstrate noninferiority with respect to a clinically relevant outcome; rather, that demonstration of performance against a clinically relevant outcome was one way of demonstrating that your antibody was function.

So because I don't believe that the sample sizes that would be necessary to demonstrate noninferiority of the clinical performance against any of these clinically relevant outcomes are readily obtained, and given how good our data are in support of the idea that antibody is the driving factor here in protection, I don't think it's reasonable to set that standard.

I think there are a couple of other questions that you raised that can be addressed. Can the study be done anywhere? Yes, but I think the manufacturers should proceed with great caution if they go outside of the United States because they're going to have to figure out how they're going to satisfy the committee that their non-U.S. data are

bridgeable to the U.S., and that's a very difficult question, one that can be avoided by not going outside the U.S.

So I don't think that's a bar we set, but I think everybody had better recognize that they put a big hurdle in front of themselves if they go that pathway.

We also need to define noninferiority very clearly. I think one of the things that's an essential outcome of today's meeting is that the companies are given a road map to licensure. Whether this comes from the FDA in six months or it comes straight out of this meeting, but somehow because these issues are so thorny, it is incumbent upon us and our FDA colleagues to insure that the companies don't spend three or four years in a developmental process that then is met here by rejection because we didn't really mean .18. We meant .30, or we didn't really mean you had to show this functional or you had to show that functional.

It is incumbent in this complex area to offer a clear road map.

And finally, I agree with what Steve said. We've got one other safeguard here, and that's post marketing surveillance for breakthrough cases. The

FDA always has the option, and this committee can always recommend that that be done, and the less sanguine we are about the strength of evidence of efficacy for a particular candidate vaccine, the more we may be likely to ask that surveillance of breakthrough cases be done to identify serotype specific failures. So that's an option we retain.

ACTING CHAIRMAN DAUM: I think caution, of course, is that this committee is advisory, and so I would think a company would be remiss to infer a road map from this discussion without input from colleagues at the agency.

Dr. Giebink, please.

DR. GIEBINK: I do believe that a noninferiority immune response trial is sufficient for inferring efficacy, but I have lots of caveats, and I must admit at this end of the table, it's hard to come up with many new caveats.

(Laughter.)

ACTING CHAIRMAN DAUM: You don't have to.

PARTICIPANT: But, Scott, I can help. Wait. I can help you.

ACTING CHAIRMAN DAUM: You don't have to.

DR. GIEBINK: But I want to emphasize a couple. I want to emphasize a couple.

As Pamela said, the bar has been set. Clearly the bar has been set, and in that respect, I believe that given all of the discussion and variance in ELISA assays that exist and the discussion that we've had, that we need to validate against the Wyeth assay. That's the assay that was used that produced the antibody results that led to licensure of Prevnar, and I think we need to -- that another product would need to bridge to that assay or at least those results.

The demographic issues of the population chosen for another vaccine immunogenicity trial is crucial, whether it's inside the U.S. or outside the U.S. The difference in demography outside is obvious.

Inside there are big differences, too, and that needs to be recognized, and the only other thing I haven't heard mentioned so far is that we have some populations in this country at exceedingly high risk of invasive pneumococcal disease and high mortality, and we should not lose sight of the fact that studies need to be done early on in these high risk sickle cell disease populations, transplant populations, et cetera, as early Phase 4 studies.

And I think just passing that along to the FDA is admonishment that those are important studies.

ACTING CHAIRMAN DAUM: Thank you, Scott.

I would, as we continue to go around the table, remind my colleagues that we don't have to just say something. Having the force of agreement with what's been said previously counts for a lot. We'll put that right in the win column.

Dr. Kohl.

DR. KOHL: Yes. For noninferiority being sufficient, again, I agree with and hope the FDA can stick to this high bar, high bar being everything that has been said, including meeting noninferiority for all seven serotypes in Prevnar, including using an assay that they judge is reliable, including setting a level of antibody that is a fairly high level, and I can't do that at this moment, but we've heard lots of different levels batted around. I'm going for higher, and I think that bar should be set higher.

I also think that we've really made things a lot easier for our pharmaceutical friends across the table in terms of if this holds, not mandating very large efficacy trials, and I think that then hopefully the FDA feels comfortable in really setting out some very, very structured requirements for post licensure study, which unfortunately we've tried to do with other vaccines, and at times haven't succeeded, and

that's come back to bite us.

I'm thinking of the Lyme vaccine, and at other times has succeeded very well. Rotavirus really has been a very good thing that's happened.

And lastly, to echo what we've said yesterday and what I know that Dr. Faggett and I feel strongly about is looking at diverse populations within this country, which are very high risk but haven't been emphasized. A black ghetto population is a very high risk population for invasive pneumococcal disease and they should be specifically included in this licensure requirement.

ACTING CHAIRMAN DAUM: Thank you, Steve. That's very helpful.

Dr. Kim, please.

DR. KIM: I want to support that noninferiority based on immune responses is sufficient for inferring efficacy against invasive disease. Again, I think an important, at least, issue to me is that, again, the assay for -- and then for this, I guess we talked about many different assays based on the other issues involved with the functional assays. I believe the binding assays, such as ELISA, would be preferred.

However, I think it is important that when

we looked at the data from various individuals or manufacturers about ELISA titers, then we really need to know that those assays are, indeed, comparable and reproducible and have been consistent with a -- if there's a guideline, they're consistent with the guidelines coming from the FDA.

And then regarding whether immune responses need to occur comparable to Prevnar, I also agree that the immune responses have to be at least equivalent to Prevnar for all seven serotypes that are contained in the vaccines because that already has been shown to be efficacious and that that is a licensed product.

And, again, I think it's also -- I'd like to see some functional activities that, you know, comparing or at least supporting the data coming from the binding assays. Again, I know the issues have not been settled. I'd like to see some more discussion going on on these, you know, assays, such as opsonophagocytic assays. I'd like to see some sort of agreement among interested parties about the assays so that certainly that would be meaningful and also it would be reproducible so that we'll be able to, you know, as a committee member, we'll be able to understand what those numbers mean.

ACTING CHAIRMAN DAUM: Thank you, Dr. Kim.

Dr. Faggett.

DR. FAGGETT: Yes. I'll start off with a caveat. As a condition, we know that laboratory data in only adjunctive to one's clinical impression, but I think I've gained a much better appreciation of some of the available tools today. So I'm very comfortable at this point to agree that noninferiority immune response trials are sufficient, again, with adequate bridging studies, including U.S. population, and that way I think we can infer efficacy of the product.

I think that the ELISA and other tests to be determined pretty much on a vaccine-by-vaccine, case-by-case basis would be the way to go, with ELISA being the most appropriate to start with.

So those would be my comments.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Griffin.

DR. GRIFFIN: Yes on the first part, and on the second part I think I've already made it clear that the ELISA I would want to be bolstered with a functional assay to show that those antibodies do have functional capacity.

ACTING CHAIRMAN DAUM: Dr. Diaz, please.

DR. DIAZ: I would agree that noninferiority would be sufficient. I think my colleagues have already addressed the areas that I'd like to emphasize, which obviously being a comparable population.

I likewise believe that there must be some functionality testing done, especially since we'll be comparing products that are conjugated to different proteins.

I feel that the bar has been set high, as was already noted, and we have a vaccine that's licensed that's extremely effective, and the bar ought to be high because this is a disease that has an unacceptable morbidity and mortality associated with it in young children.

So with that in mind, in answer to the question of what would we do if one of the components did not reach noninferiority, I would agree that they all should, notwithstanding that the door would not be shut, as was pointed out prior in terms of doing efficacy studies down the line, but that in terms of looking for noninferiority, that all seven should reach that criteria.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Katz.

DR. KATZ: I'll not try to measure up to Michael Decker, but I'll make a speech, too.

(Laughter.)

DR. KATZ: First of all, I don't like the term "noninferiority." I'd rather say "equivalence." It seem to me noninferiority is negative and pejorative almost. I would vote yes for equivalence.

But I'd like to take one second or two just to comment on a meeting that we attended several weeks ago at CDC, where we learned that there's a shortage of tetanus-diphtheria vaccine. One company is dropping out of DTAP. We had a delay in the availability of influenza virus vaccine this year. Cholera and typhoid may no longer be available, at least certain products.

I see a great fragility in the vaccine system which concerns me greatly, and I think we should be doing everything possible within scientific relevance to encourage the development and the availability of these vaccines.

Another feature of these vaccines that excites me is that they'll be beneficial to the developing world and not just the United States.

We lost Rotavirus vaccine where we have that same excitement that we had something that would

be helpful to children throughout the world. So that I think we should do everything possible with appropriate scientific caution to encourage this.

So that I would vote a strong affirmative yes, and on the second part, the same caveat that Diane expressed, that the immunologic parameters by ELISA be confirmed as having functional capability also.

ACTING CHAIRMAN DAUM: Not least.

DR. GOLDBERG: I think that noninferiority trials are necessary. I don't think in and of themselves they are sufficient. I do believe that there are some ways to get to do some efficacy trials here.

I've already discussed that. If we were to go with the, quote, noninferiority trial, I think it would be incumbent that every component be sort of identical, and by that what I mean is that I think ten percent is too big a window, which would then increase the size of your trials, give you more safety data, and make these immunologic trials considerably larger in size and at least begin to get at some of the safety issues and begin to give you a little bit more of a feeling that the vaccine might be in the large safe.

Now, I really believe that some legitimate attempts should be -- careful attempts should be made to develop the efficacy trials in some newer paradigms, and they won't be precise efficacy trials in head-to-head comparisons of the kind that were done originally, but with broader endpoints, recognizing that what you're looking at is for a clinical impression of the vaccine in a comparative way, and I do believe that should be possible.

And you will at the same time be accumulating pre-marketing safety data.

DR. GOLDBERG: Thank you, Dr. Goldberg.

I am last, and probably also least, but a couple of comments before we finish this discussion. My basic view is that the answer to the question from my point of view is yes, that I would accept that, and I do share the comments that were made that it has to be a head-to-head comparison. I'd be upset if anyone tried to do this with historical information, and that the population has to be relevant one to the United States if that's where it's going to be licensed, and ideally should incorporate many of the groups that we have that re ethnically divers, although I note that the trial that established this efficacy was largely done in a middle class, HMO type population in

Northern California. So we don't have that information about this vaccine, although the Navajo trial has helped insure that bridge very nicely.

I think the most important thing that I would like to add is that we not be rigid in how we set up parameters here, and that's a hard thing to come to grips with because the companies want guidance. The FDA wants our guidance, but I don't think it's time for rigidity. I don't think we have all the information we need to offer rigid guidance.

For example, some of my colleagues have said that all seven serotypes need to be there, and we need to be noninferior, but yet, as Dr. Siber pointed out earlier, three of the serotypes, in fact, don't have clinical efficacy and didn't have in the trial. So what do we do with those?

I would like to see a trial set up with a noninferiority -- forgive me -- kind of design, but I'd like to use the committee's expertise and the fact that we've all been to school and have higher education and all of the groups in this room that want better health care for kids, and interpret them with some common sense.

So that if, for example, there was one serotype that didn't measure up and it wasn't a major

cause of disease and it wasn't one of the ones we've had antibiotic resistance trouble with, we might not be too upset with that.

On the other hand, if we had a big failure of one that was a major cause of disease or major antibiotic resistance problem, we might take a different view of that.

And so that's a brave and uncertain new kind of world, but I think it's sort of where the state of the art is right now, and I'm not sure devising a weighting system -- I can see the discussion two years from now, that we do a weighting system where this type counts for more because it causes more disease, and then it misses by .1 points in our weighting system, and we're going to throw it out then.

I think that's too rigid for the state of the art of the knowledge.

In terms of assays, we're in some trouble here because we don't have the correlates we want. The trial was such a fantastic success that we didn't get the correlates we wanted because they weren't failure patients to really get that data from.

I'd like to see the otitis media data, but I'm not sure how relevant it's going to be to invasive

disease, and I think we're going to have to sit down and interpret and see what we think of those.

ELISA sounds like the closest thing we have to a working assay. I think we've got to put some weight on it even though it's got lots of problems that we've heard over and over again. I'd like to think that we could develop some kind of functional assay to go with ELISA numbers. I'm convinced after listening to this discussion that we don't know how to do it.

I think probably the best bet is some kind of opsonophagocytic assay, but I'm concerned about some of the things that have been raised with low titer serum. I think we need better assays and better methods for doing this, and I turn to NIH colleagues to keep supporting work and to how to do this better because we're nowhere near.

Avidity is an idea whose time has sort of come, and it's a very exciting concept, and I'm hearing lots of interesting things about it, but I don't know how to use it clinically yet, and I'm not sure that I want to put my weight on that.

I want to echo a comment that Dr. Broome made, I think, when we went around, and that is that we don't know enough about these different serotypes

to do any kind of pooling yet, and I would be really upset if we didn't continue to consider these seven different problems.

And it may be that after we gain some experience that we'll find that they're remarkably similar and that pooling is just the right thing to do, and it may be that when we finally understand why 19F is the funny serotype that it is, we'll realize that pooling wasn't the right thing to do.

I don't think it's time to do the pooling now.

Lastly, I would like to say that whatever vaccines are put into play in this regard, there's some important issues here that have got to be addressed with post marketing surveillance and studies, and several people have called for them. I don't have any things to add to what's been said, except the possibility of antigenic shift, which I think is a concern that hasn't been completely addressed yet, and we need to know whether it's going to occur or it's not.

And I think the committee did a wonderful job addressing this question, and I would propose that we reward them with a short break, 15 minutes in duration, and reassemble at 3:15 to go right into

question tow.

(Whereupon, the foregoing matter went off the record at 2:59 p.m. and went back on the record at 3:16 p.m.)

ACTING CHAIRMAN DAUM: There are a number of committee members with obligations late this afternoon, and which is unfortunate for us because we need to keep as much of a quorum as we can to finish discussing these issues, but I would like to also be a realist and try and move things along a little bit more quickly so we can get as many people's opinions on as many of these issues as we can.

So we're going to go right on to the next issue, and I hope it's up there. It is. Thank you.

Please discuss the criteria that should be considered to evaluate serotypes not contained in Prevnar.

And is Dr. Broome here? She expressed some interest in starting this conversation, but if not, we'll start with Dr. Kohl.

DR. KOHL: Well, since the other one was so easy with some data, this is a piece of cake with no data.

(Laughter.)

DR. KOHL: I'd like to say that we would

need clinical efficacy trials to have licensure of these serotypes, and I believe that's unrealistic because we're getting into the rare, rare serotypes now, and you'd have to have a gigantic study, I guess, in this country, and that's not possible.

And then if you went to another country where maybe these serotypes are more common, you've got all the problems of doing a study in another country.

So I'm going to have to fall back and say I probably would be satisfied with some immunological correlates, and then I'm lost because I have zero data on which to say what correlates, and I haven't seen anything that's come forth to suggest what they should be.

So can we pull an ELISA value out of a hat or do exactly what Claire said not to do, which would be to lump all of those other ELISA data values and say, yes, let's use point-something-something?

I'm a little bit lost here.

ACTING CHAIRMAN DAUM: Okay. There's a little logic missing there, Steve. Someone as we go around the table is going to have to fill in a little better as to what correlate we use if we go the route of non-efficacy trials, but let's see what going

around brings.

Dr. Kim.

DR. KIM: Well, I guess in contrast to what Steve said, I think it will be extremely difficult if these serotypes are contained in the new vaccines simply to expand the spectrum of serotypes for asking any clean-cut or efficacy data.

Therefore, I think my thinking at this time would be some sort of immunologic data can be substituted to indicate that the serotypes may provide functionally active antibodies which can be translated into possibly clean-cut efficacy.

I think for that, I think it is important to perhaps in this question we can include assays on a sort of equal basis. In previous discussions, questions we talked about ELISA for the, you know, many reasons, for the simplistic reproducibility and so on, but here we may not be able to do that because there's no data to indicate that.

So we may have to include binding as with functional data to indicate that perhaps both in vitro and in vivo -- in vivo means animal model -- to indicate that antibodies produced by these serotypes are at least equivalent to serotypes that are contained in the existing vaccines for magnitude of

responses, as well as functionality of those antibodies.

ACTING CHAIRMAN DAUM: And the bottom line is?

DR. KIM: The bottom line is it would be immunologic criteria can be used to assess the sera.

ACTING CHAIRMAN DAUM: Okay. Dr. Griffin, please.

DR. GRIFFIN: Well, I'm not going to be any more definitive, but I guess what I'm struggling with is the practicality versus what you'd really like to have and also what that means downstream if you go from 11 to 15, you know, subsequently and that sort of thing.

And I guess it's really not possible. Any kind of a trial that would get clinical efficacy would be comparing Prevnar to, say, an 11-valent vaccine. So you'd have four serotypes that weren't there. So you'd have that way a placebo controlled trial in a way looking at those.

But those would be so infrequent that you really would not be able to power the study probably to be able to see the clinical efficacy there, certainly for invasive disease. Whether you could for otitis or not, someone else would have to tell me.

So in the U.S. that would be the only kind of study, it seems like, that you could talk about.

Outside the U.S., whether it's still feasible to do placebo controlled trials, perhaps not just because of Helsinki conventions, even though standard of care in other places may not be using Prevnar in the same way that we are. They would still be fairly large trials.

So I think we're probably stuck with the immunologic assays. I would definitely say you'd need function as well as ELISA activity, and I guess I would just like to see built into any of these studies some attempt to get clinical data.

ACTING CHAIRMAN DAUM: And what immunologic criteria, Dr. Griffin?

DR. GRIFFIN: Well, we've only heard about two assays.

ACTING CHAIRMAN DAUM: Right, but we've heard about many different estimates of --

DR. GRIFFIN: So I would want both of them.

What?

ACTING CHAIRMAN DAUM: We've heard many different estimates of protection. I mean, how would you select one serotype? Supposing you added a type

99 and 100 to the vaccine. What immunologic parameter would we use to assess whether they are efficacious?

DR. GRIFFIN: You have no immunological parameter other than comparing them to what you know about the other serotypes unless you set up an efficacy study.

ACTING CHAIRMAN DAUM: Okay. Dr. Diaz.

DR. DIAZ: I think you'd have to go with immunologic criteria also, and I agree I would want to see some data on functionality and whether immunologic memory ought to be part of that package deal is debatable, and certainly some level of antibody, although I don't know what that level is currently.

I would feel more comfortable with some clinical data behind it, and yet that would take a huge number unless perhaps there is some population somewhere that that particular serotype was more prevalent in and that data could be accrued.

But that perhaps not occurring, I think we'd be left with immunologic.

ACTING CHAIRMAN DAUM: Dr. Katz.

DR. KATZ: I'm a little concerned about what things I heard in the closed session versus what's been discussed here. So I'll have to be circumspect in my response except to say I would say,

yes, the immunologic criteria would be satisfactory, given some of the numbers we've heard.

However, and I don't know how feasible this is, one of my other jobs is co-chairing the India-U.S. Vaccine Action Program. There are 23 million children a year born in India, and if it were feasible from the pharmaceutical firms' perspective to set up a study, that's a population with more than enough children and with the serotypes that are being added to the vaccine apparently among those responsible for disease.

I wonder if a study couldn't be done through a program such as the so-called VAP, Indian-U.S. Vaccine Action Program, where either with Prevnar as the alternative or with a vaccine, one of the meningococcal vaccines or Hepatitis B or Hepatitis A or any of the other vaccines that would prevent diseases that are common among those children as the alternate.

ACTING CHAIRMAN DAUM: You're arguing for an efficacy trial in a developing country or in a non-U.S.

DR. KATZ: I'm not arguing for it. I'm suggesting it and sort of looking at our pharmaceutical colleagues to wonder if that's

something they would consider.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Goldberg.

DR. GOLDBERG: I thought we should have an efficacy trial before, and this certainly says to me that we need an efficacy trial.

ACTING CHAIRMAN DAUM: For the novel serotypes?

DR. GOLDBERG: That's right, which if you did a trial compared to Prevnar, that means these 11 valent vaccines would be randomized again. Patients would receive the 11-valent vaccine versus the Prevnar.

ACTING CHAIRMAN DAUM: Okay. Thank you very much.

Dr. Insel.

DR. INSEL: I would go with an immunogenicity trial. I think we know the basis of immunity here, and it's antibody. I think we can learn; we have learned from the Prevnar.

Having said that, then one is forced to say, well, what are those criteria that one's going to use. I think as far as we go back to the ELISA assay, we're going to have to, I believe, set a threshold a

little bit differently than what we've set for the vaccine serotypes for which we have efficacy data.

We'd want to set that threshold, I think, higher than what we've done just so we don't err.

I would also ask for functional assays, and I'd ask for proof that we have primed for responses to a polysaccharide vaccine for these serotypes that are not contained in the Prevnar.

DR. WHARTON: Given that the excellent clinical trial that was done pre-ELISA for Prevnar, in fact, did not establish efficacy for all of the serotypes contained in that vaccine, I would not impose that standard on an increased valency vaccine demonstrating efficacy for all of the serotypes in an effectiveness trial.

I'm comfortable going with an immunogenicity study using a preestablished threshold. I agree with Dr. Insel's comments that that threshold needs to be established conservatively.

I'm still very interested in the presentation which I didn't hear at the pneumococcal workshop last month about the BPIG data, and I really wonder what's in there that might have some lessons for us about thresholds for other serotypes of pneumococcal disease.

I also think the issue of priming is important, and I think that's an immunological criteria that could be readily established in a trial.

ACTING CHAIRMAN DAUM: You should know that I looked for you to start off this conversation.

DR. BROOME: I think immunogenicity is the right criteria. I would vote for a margin of error threshold, functional activity and priming.

I would like to make one comment on efficacy studies. I really think the kind of sample size required to do efficacy is extremely large, and you know, I think to advocate an efficacy study should be based on some sort of consideration of what's really involved with that.

I do think when we looked at question one we sort of didn't get back to the point of if nonequivalence is not shown. I mean, I guess we'll pick that up in question four, but I do think when we say nonequivalence is fine, I would assume folks are also going to recognize that just in case they don't meet nonequivalence, it might be a good idea to have the efficacy trial going.

ACTING CHAIRMAN DAUM: I think I heard that in a number of comments people made about question one, but thank you for emphasizing it.

DR. BROOME: But I'm assuming that would not be in the U.S.

ACTING CHAIRMAN DAUM: Correct. Certainly not for a placebo controlled.

Dr. Butler.

DR. BUTLER: I'm struggling with this idea of another efficacy trial. I'm not sure if you meant in the U.S. or not, but -- okay, good. Because if we're talking about specifically for the additional serotypes, the power calculation just becomes ridiculous.

I think the goal with the additional serotypes, the ones that are achievable are to prevent the case of invasive disease caused by those serotypes which are not contained in Prevnar. Another advantage will be less replacement disease in terms of colonization and presumably also acute otitis media.

If we could assume that the safety profile is similar for a newer vaccine and that there's no increased risk of disease, some of the data for the additional two or four serotypes becomes almost irrelevant in that these gains would be icing on the cake if you show noninferiority.

I think ultimately it's going to come down to immunologic criteria. Some of that is going to be

based on the epidemiology of the serotype. If I can return to my hypothetical vaccine that fails on the basis of inferiority of immune response to serotype 4, if a candidate vaccine showed a good immune response to serotype 1 in certain populations -- certainly it's true in Alaska -- it may be more attractive.

I'm making the assumption again that we would not be able to identify efficacy. Therefore any correlate of protection would be based either on the Prevnar serotypes or would be nonexistent.

The other immune criteria that I wanted to mention because I haven't heard it mentioned so far is the impact on immunogenicity of co-administered antigens. We've focused primarily on serotype, but the newer vaccines oftentimes have different carriers, and if it reduces immunogenicity of the co-administered Hib antigen or enhances it, those are important considerations as well.

ACTING CHAIRMAN DAUM: Good point. Thank you.

Dr. Hall.

DR. HALL: Well, there's not a lot more to add to this. One of the points I was going to make Jay just made, but I think everybody would like an efficacy trial. To repeat this, it's probably not

practical, particularly for invasive disease either in this country or in another country with these serotypes unless there is a country that has the additional serotypes enough to judge the invasive disease.

So that the immunologic criteria, I think, again come up as being probably what we're going to have to go with.

The only thing that I wanted to really add and that you had sort of mentioned, Jay, is that we are, therefore, in an efficacy looking potentially at other associated factors. One of those could possibly be carriage.

Now, that would require that it be used, since we know it's going to be different in different populations, that it might be matched to prevnar in the same population.

Now, I don't know that that's a secondary effect that would be usable, but it's one possibility. Another are the other things such as the effect on antibiotic resistance and other things. And if you put these two vaccines head to head, if these secondary findings come out different, that may influence one, besides the immunologic one that Jay mentioned.

ACTING CHAIRMAN DAUM: Thank you, Dr. Hall.

Dr. Emerson.

DR. EMERSON: I just would concur with the statement that was made earlier that this is really a problem that's been solved before in the sense of the Prevnar case, that we had some that we couldn't demonstrate efficacy for, but the indication still came out with all seven serotypes.

I don't think it very likely that an efficacy trial is really worthwhile to try to establish efficacy against one of the rarer serotypes, and therefore, my side would come down as I would have wanted to see a trial that was demonstrating efficacy on overall pneumococcal invasive disease, and then just commenting on the immunologic profile against the serotypes and not really trying to claim that you have prevented that or not.

Certainly in this immunologic profile, however, I think the data should be gathered as to whether there was any sort of invasive disease breakthrough, and I don't care what the immunologic profile is. If it's not backed up with prevention of those particular serotypes, that is to say if you get some serotype breakthrough, I would not give the

indication in that situation.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. McInnes.

DR. McINNES: I'm thinking about this in two ways, one of which is additional serotype to the already licensed serotypes, and then a new conjugate vaccine that may contain additional serotypes, and those two scenarios may play out differently in that the new vaccine may go through an efficacy trial, and I'm going to learn from that, and I don't know what's going to come to the table first.

But it strikes me that pragmatism has to play a role here, and you're going to look at additional -- you have a core group of serotypes fitting the existing vaccine selected on epidemiologic basis largely as the most important serotypes.

We have the sort of second tier now that we think are important, and we'd like to see included, and practically speaking, the manufacturers, I think, are going to want to be dealing with those concentrations that are very close to the individual serotypes that are already in the vaccine.

So let's assume you have two micrograms of A, B, C, D, E, F, and I'm now wanting to add G. So I

pragmatically go and I say I'm going to have two micrograms of that, and I do some immunogenicity, and it looks pretty good or I don't get anything.

So what choice do I have? I can up the ante on the dose concentration of the new antigen that I put in, and essentially I get what I get in terms of immunogenicity data.

If the bar is very high, I now have to weigh whether I'm going to continue to putz around on antigen G or whether I'm just going to forget about it. I've not had it in my vaccine.

So I think we have to be pragmatic about the bar we're setting for the addition of new serotypes unless there becomes some compelling reason to understand that that bar set very high is very important for safety purposes or efficacy purposes, and to some extent, you know, to guess is cheap and to guess wrong is very expensive.

I'm heading towards trying to embrace the concept of an aggregate bar thinking about additional serotypes, and I think of it differently than a vaccine that has gone through an efficacy trial in the serotypes contained in that particular vaccine.

So I'm embracing the concept of immunogenicity being used and being valid. I'm

vacillating about the standard that I would set for those particular serotypes, and I think pragmatism has to play in. Otherwise the incentive to add additional serotypes if problematic.

ACTING CHAIRMAN DAUM: Thank you. You made a couple of points that haven't really been addressed before.

Dr. Decker.

DR. DECKER: I think the circumstance that we're discussing here is that we've got a vaccine that has presumptively already met whatever criteria we end up requiring or FDA ends up requiring with respect to question one, and what we're now addressing is the marginal criteria that apply to these additional contained serotypes.

And given that that's what we're discussing, then I agree entirely with Dr. Insel that this should be serologic. If we were to require a demonstration of efficacy for those marginal serotypes, we would basically be precluding licensure of a vaccine line this in the United States. There would be no point in bringing it forward. There's no economic or competitive reason to do that in the United States. Therefore, it won't happen. It will simply be licensed overseas.

And the seventh serotype will be licensed here. Now, I see no benefit in denying U.S. kids those additional serotypes, and so I feel strongly that we need to have an immunologic criterion for licensing these additional serotypes.

In that regard, the approach indicated in the FDA's presentation, slide eight, the maximal difference of GMC which showed the RCDs for the immunized and the unimmunized kids and developed the point where there was the maximal difference. I think that's a sound approach. It was endorsed pretty thoroughly at the meeting on the 26th, and although there's been some slight discussion over what's the appropriate number to use -- .18, .30 I've heard discussed -- that's a technical issue to be decided. The basic approach, I think is solid.

The question then becomes: how do you do this for these serotypes that weren't in the -- for which we don't have efficacy data that were not in Prevnar in this study?

I think you simply take your best number, and you apply it to these other serotypes, which in essence is what was done for the other three serotypes and Prevnar, and you proceed on that basis.

ACTING CHAIRMAN DAUM: Thank you.

Before I comment, I actually have a question that I hope the manufacturer, Wyeth, can update us on.

There is, is there not, a trial going on now in South Africa with a more than seven-valent vaccine? Can someone in just one or two sentences say what that is and where it's at?

DR. WATSON: Wendy Watson, Wyeth.

Yeah, there is a trial going on in South Africa with a nine-valent vaccine. It has the seven serotypes from Prevnar, as well as a one in five as being compared to placebo.

We finished the enrolling subjects in September of this year. We're in surveillance. So we expect to have more data by a year from next September.

ACTING CHAIRMAN DAUM: Endpoints are invasive disease, Wendy?

DR. WATSON: Right. That's the primary endpoint, yes.

ACTING CHAIRMAN DAUM: What about otitis?

DR. WATSON: No, no otitis. This is Soweto, South Africa. So we're looking at HIV and HIV infected and uninfected subjects.

I will say that while there are more

serotype 1 disease and 5 disease in the African continent, we're not going to -- we won't have enough cases to look at those individual serotypes. So I think even in this, I think this highlights the serotype specific efficacy is very difficult to capture.

DR. GRIFFIN: How large is that trial?

DR. WATSON: Forty thousand.

ACTING CHAIRMAN DAUM: Okay. Well, thank you very much for everybody's comments.

Dr. Goldberg, did you want to in one sentence clarify?

DR. GOLDBERG: Yeah, I just wanted to clarify. When I said efficacy trial, I was thinking in terms of a trial such as the one that was described here, not another trial within seven and seven.

ACTING CHAIRMAN DAUM: Okay. Thank you.

So I also share the theoretical ambitions of several of the committee members in that I would really love to see efficacy data for new serotypes that are added to this vaccine, and I'm sure if Ms. Fisher were here she would say that , you know, you just can't start using the stuff if you don't know that it works.

And she's right, even though she didn't

say it. On the other hand, we do have a special situation here. I mean, I guess I'm putting a lot of weight on the fact that we know that anticapsular antibody works for protection against other pneumococcal serotypes, and so we're going to close our eyes and take a leap into the pool and say, "Well, it will work against these new pneumococcal serotypes as well."

But they're not easy questions, and I think the efficacy trials are expensive probably beyond the means that society is willing to pay to do them.

There is enough data to suggest that it's likely that antibody to the capsule will be protective, and I guess it's a question of deciding how much. And I would urge that the approach be a conservative one, and I've heard several good ideas today. I don't know which is the best.

One is this RCD approach that Michael reminded us of. Another is using one of the lower GMC estimates in the existing trial. I have some issues of vaccine antigen interference to think about as we add serotypes to the vaccine, and I would hope that they'd be part of a consideration for a larger vaccine.

And that is to say as we go to eight or nine or ten or 15 or 90, will there be interference with the response of the seven that we have, and we haven't mentioned that much, but I think that it's an issue for a bridging trial of some sort.

I'm also concerned about antibody to the carrier and potentially some suppression based on cranking up the levels in a many, many valent conjugate vaccine, very high. And I think that can be dealt with, but I think it needs to be part of a trial, a serologic trial to establish going forward with this.

I also think that Dr. Butler's point is a crucial one, and that is that we need to consider the other vaccine antigens that are scheduled for simultaneous admission -- excuse me -- administration, and make sure that there's not interference in that regard.

I think the issues that people spoke of of wanting to see priming, of wanting to make sure that antibody that's generated is functional are very important and need to be done.

I'm with Dr. Hall on the importance of carriage in these studies. I don't know quite how to set up a bar that a vaccine would have to jump

through. I think there isn't any to set up for a licensure prerequisite, but I would like to see it part of a study because I believe it's a very important part of how Hib vaccines work and protect our children and our population.

So with that having been said, I'd like to go on to number three, and I'm mindful of the fact that people need to go, and I'd like to try and get some discussion on all of these questions as quickly as we can.

Number three is invasive disease efficacy study may be performed in a non-U.S. population with a new vaccine, and there's two parts to this. If efficacy is demonstrated, could data derived be used to support licensure of the vaccine in this country?

And then if the answer to that is yes, what are the immunologic parameters that should be used to establish comparability to Prevnar in a U.S. bridging study?

I'm going to this time ask Dr. Broome to start and Dr. Emerson to go next, and if someone else who has to leave signals me that they need to go, we'll put them up next, and then we'll go around the table.

Dr. Broome.

DR. BROOME: Well, I mean, I think that there will hopefully be data from efficacy trials outside of the U.S., as we've heard, from South Africa and others. And I think that we would be remiss not to pay attention to that data as we wrestle with the issues related to licensure of the vaccine in the U.S.

And I think this whole issue of how do you bridge is quite complex as we've heard with the different responses in different populations.

But I think that reasonably sized bridging immunogenicity studies should make it possible to look at presumably primarily ELISA responses in the two populations and let you learn something.

I think one of the issues that's going to be very important is I think Prevnar is obviously highly efficacious as we've seen with H. flu. conjugates. You know, how much is enough?

It may well be that -- I think the thing that will be tough is if we have something where there is a nonequivalence with Prevnar, but you do have efficacy data in another setting. I think there'll be need for a lot of judgment, but I think it's reasonable to take a look at that and see that as an alternate route for licensure.

ACTING CHAIRMAN DAUM: Would such a trial

be compared to Prevnar or would it be placebo controlled?

DR. BROOME: Do you mean the bridging?

ACTING CHAIRMAN DAUM: No, the efficacy.

DR. BROOME: The efficacy studies. Well, many of the ones that I'm familiar with were started before Prevnar was a licensed product, and so they're using other kinds of active control vaccines, but not a pneumococcal vaccine control.

I was toying with whether you'd like to do the bridging immunogenicity studies with a Prevnar arm in both countries so that you'd have that additional two data points.

ACTING CHAIRMAN DAUM: Would make interpretation a little easier, wouldn't it?

Thank you.

Dr. Emerson.

DR. EMERSON: I think certainly it would have to be allowable as support, and the question is how compelling support would be there. I would think with the serotypes that are covered in Prevnar, I think the standards for the immunologic picture would have to hold sway, and the issue would be safety.

I guess I would imagine that this would come up more with the idea of adding new serotypes,

and then the preeminent question in my mind would just be is it safe to add those additional serotypes, and looking at the safety profile, making certain that adding those serotypes didn't alter the primary ones that are already in Prevnar and immunologic standards if that's what's being adopted for addition of other new vaccines. You'd have to make certain that it passed those hurdles here.

ACTING CHAIRMAN DAUM: Well, it may not involve adding new serotypes. I mean, for example, supposing Company X wanted to get some data about the performance of their vaccine and it was a seven-valent vaccine and so they decided to take it to "Southwestia" and conduct a clinical trial.

The question really is once that trial was established, would you accept the news that that vaccine is efficacious as appropriate for U.S. licensure.

DR. EMERSON: Well, I think with the data that's been presented on the question of how generalizable the immunogenicity is of these serotypes, my answer would be no, and with the decisions that have been made beforehand, it's saying that it's unlikely that we'll have evidence on the correlates to be able to do anything more than just

apply our standards for a new vaccine.

ACTING CHAIRMAN DAUM: Thank you very much.

I think now we'll go our conventional route and come to Richard and then go up the side here and swing around.

DR. INSEL: Not much to add except the bridging and immunogenicity studies will be required. Some of the issues that can arise obviously are the issues of colonization and priming that's occurring at another locale outside the United States versus what's going on in the United States and what this would add to as far as enhancing immunogenicity.

So I think as long as we have immunogenicity bridging trials, and I think Claire's idea of doing them in both settings, I think we'd be reassured that we're on the right pathway.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Wharton.

DR. WHARTON: Yeah, I would support such data. I would accept such data in support of licensure, and I really like the idea of doing a Prevnar-new vaccine bridging study in that country as part of the bridging assessment.

ACTING CHAIRMAN DAUM: Dr. Butler.

DR. BUTLER: I have little to add on this topic. I think it's hard to make broad statements. Clearly there are differences in the epidemiology, probably differences in the immune responses to the vaccine.

The joke we sometimes throw around is everything works in Finland.

(Laughter.)

DR. BUTLER: And there's some truth to that. Some of that is driven by socioeconomic factors, of course. So I think it would be wrong to ignore data from non-U.S. trials.

At the same time, the Gambia would be very hard to apply to an HMO population in the U.S. So I think it's really going to be on a case-by-case basis.

ACTING CHAIRMAN DAUM: But as a generic concept, if the study were performed and efficacy was demonstrated, you would agree or disagree with the fact that data derived from such a trial could support licensure in this country?

DR. BUTLER: I would agree that it could support.

ACTING CHAIRMAN DAUM: Good. Thank you.

Dr. Hall.

DR. HALL: I would also agree that it could support it. Indeed, in some instances, depending on the country, it may actually show more efficacy, if I may say so, in that particular country. It may have been more difficult to get a response.

I think the second -- the immunologic criteria that could be used or should be used as mentioned would be further supported if we did have the comparable data in that country on the Prevnar.

ACTING CHAIRMAN DAUM: Yeah. That strikes me as a very clever idea actually to solve that problem.

Dr. McInnes.

DR. McINNES: I have nothing to add. I accept the efficacy trial, but I don't see any reason not to, and the bridging study as all have previously described in question one.

ACTING CHAIRMAN DAUM: Dr. Decker.

DR. DECKER: A, absolutely in principle, but the devil is in the details, and some of them have been brought up.

The one thing I don't recall having heard mentioned is that I think it is my suspicion the committee would end up requiring serotype specific efficacy. That is to say if a study were done in a

country in which the serotype distribution were marked different from the United States, and if overall efficacy was demonstrated, there would be concern that that efficacy was predominantly against serotypes not prevalent here.

We would want to see that there was efficacy against the serotypes that circulate here. So I suspect that that would be a hidden question here, that companies interested in doing studies overseas had better be alert to.

The other consideration is that, of course, there has to be the bridging data, and it would be impossible to interpret those bridging data unless, as others have said, there was a Prevnar versus candidate both in the other country and in the U.S. to enable us to set up ratios.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Kohl, you're on.

DR. KOHL: I basically agree with everything that's been said, but it comes back to an issue that Dr. McInnes raised. What will we do if we have a vaccine that has really super efficacy in Country Z and then we have a bridging study which we won't even need the efficacy study if the bridging

study shows high immunogenicity in this country because we've already said immunogenicity alone is going to be okay for licensure.

But what do we do with this vaccine which has wonderful efficacy, but has poor immunogenicity in the bridge? What would this committee do?

It protects super against type Q, but it doesn't make antibody, but it's not likely, but that's what we're talking about, and that's the issue that Dr. McInnes raise.

DR. DECKER: But I think the two arm bridging study in each country answers that because you'll take the ratios.

DR. KOHL: Okay. So if it doesn't make antibody in Country Z and it doesn't make antibody --

DR. DECKER: And it equally doesn't make it here.

DR. KOHL: Right.

DR. DECKER: Then you're okay.

DR. KOHL: Then we'll license it?

DR. DECKER: Yeah.

DR. KOHL: Even though type 6 is very common in this country? I think we'd have trouble with that.

DR. DECKER: Well, no, you might be type

specific, but if the ratio of antibodies --

DR. KOHL: Type 6 is a common type in this country, right? It protects against type 6 in whatever country they've tested it in, but for some reason it doesn't make antibody or has a different kinetics of antibody and we don't see it after dose three or something crazy, and the same thing happens here, protective, but nonimmunogenic. I doubt that that's going to happen, but it's something to think about.

Because if it makes antibody well, then we don't need the efficacy study. We've already said that all you need is immunogenicity. So we're talking about something that doesn't make antibody well.

ACTING CHAIRMAN DAUM: On the other hand, efficacy is gold.

DR. GRIFFIN: Efficacy trumps.

DR. KOHL: Seriously. No antibody and you'll take efficacy.

ACTING CHAIRMAN DAUM: Efficacy is gold.

Dr. Kim.

DR. KIM: Well, I think if the efficacy is there, then it is likely that it could have immunogenicity data supporting efficacy, and if the new vaccine contains serotypes that are contained in

Prevnar, then I guess certainly, you know, you can look at efficacy and immunogenicity data of those serotypes that are contained in Prevnar, which certainly would be the basis for transporting the data directly to the U.S.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Griffin.

DR. GRIFFIN: I think we should definitely accept support data that's collected outside of the U.S. could be very helpful, and that bridging would be immunologic bridge for comparability of antibody.

DR. DIAZ: I likewise feel that any clinical data, efficacy data from outside the U.S. could be very helpful, and in fact, although we've already said that noninferiority studies would be sufficient in this country or in comparable populations, I still have the caveat of saying that I would feel more comfortable with some efficacy data. I mean, it would add to obviously and be supportive of and perhaps supersede those noninferiority kinds of studies.

That already being said, I think you have to be very careful what population is chosen outside the U.S., and the bridging studies obviously would be very important.

I hope, and I would expect that we'll be back in this room probably discussing all of the nuances of every outlying vaccine or serotype issue that comes up down the line. I would hope though that when we're back in this room discussing that that we have more information on protectiveness and more information on the immune response.

And certainly having more monies and attention directed in that area is extremely critical, I think, at this time.

ACTING CHAIRMAN DAUM: And then Dr. Katz. Dr. Katz?

DR. KATZ: Dr. Katz was having his four o'clock drowsy spell.

ACTING CHAIRMAN DAUM: Fair enough. I understand the feeling.

(Laughter.)

DR. KATZ: I'd be very happy --

ACTING CHAIRMAN DAUM: We're here in the Versailles Room, and we're talking about --

DR. KATZ: No, no.

(Laughter.)

DR. KATZ: I think that if an efficacy study is feasible in a non-U.S. population, it could be done, but I don't think it should be a criterion

before licensure. It might be a Phase 4 rather than a Phase 3, and I do think that efficacy demonstrated elsewhere could be bridged to the United States, given that these are unusual serotypes and we don't know what may happen with nasopharyngeal carriage and the emergence of other serotypes. I think it would be worthy to have them licensed in the United States.

And, again, I would use the same immunological parameters that we used for question two.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Goldberg.

DR. GOLDBERG: Yes, you can use the data in the U.S. I would have a Prevnar arm, and I would use that in the bridging.

ACTING CHAIRMAN DAUM: And I would end by agreeing totally that of course they're useful. Efficacy is gold, and whether it makes antibody or not, I mean, if you've got demonstrated efficacy in a carefully done trial, it works.

and then I would like to have it bridged to American kids, and I think Claire's idea of having Prevnar in the trial to help with the bridging is superb, and I would encourage anybody, any company that wants to conduct such a trial in a developing

country, that we'd be very interested in hearing the results.

Let's move on to question four and try to race for the finish line here. We'll put it on the screen.

Please discuss if data demonstrating clinical efficacy against acute otitis media for a new pneumococcal conjugate vaccine can also be used to infer efficacy against invasive disease.

And this is not an easy question. Dr. Kohl, would you like to start answering it?

DR. KOHL: I did so well on the last one.

I don't think it can. I think most likely otitis media is a stronger challenge than invasive immunologically, but I'm reluctant to say that otitis media data can be used to license an invasive pneumococcal indication.

ACTING CHAIRMAN DAUM: Okay. Dr. Kim.

DR. KIM: Well, based on the information provided to us today, I'm not sure that we'd be able to say that efficacy data for otitis media can be directly translated into that against invasive disease.

Also, it is an interesting idea. Certainly I think it needs to be further explored.

DR. GRIFFIN: Well, I think this is a question on which intuitively I would say yes, that it's highly likely that it's going to be predictive. I think it's a question though that we're going to have more data on as time goes on from data analysis of trials that have been completed, and so we might have a stronger leg to stand on.

But if it's an antibody mediated process, then it probably requires more -- we've already heard that it probably requires more antibody at least in animal models, more antibody in order to accomplish this task.

But then you would anticipate that you would also be protecting against invasive disease.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Diaz.

DR. DIAZ: I would say de novo that, no, it cannot be used for criteria for invasive pneumococcal disease efficacy, although I guess there are other caveats to that. If we're dealing with a vaccine that has the same serotypes as Prevnar and we're looking at, as an example, noninferiority for licensure for noninvasive disease, having data on efficacy for acute otitis media would be very

supportive in my mind because I would have efficacy against at least some component of disease caused by those serotypes.

So although I don't believe for, as an example, a new serotype additional serotypes that are not in Prevnar to be able to use efficacy for otitis media to bridge to invasive disease, I disagree strongly. But I do think date about otitis media can be very supportive in looking at licensure of products for invasive disease with comparable serotypes to Prevnar.

ACTING CHAIRMAN DAUM: Thank you.

DR. KATZ: I'm sorry Dr. Giebink had to leave because I was impressed with his comment from his chinchilla model, but the antibody data to prevent otitis were higher than those to prevent invasive disease. I would like to see that extrapolated further, obviously into human populations, and I would have to agree that otitis data alone would not be sufficient to infer efficacy against invasive pneumococcal disease, but would be very, very prejudicial towards it.

DR. GOLDBERG: I believe that you can use the same trial and define a series of endpoints that would cover invasive pneumococcal disease, acute

otitis media, and the other endpoints that were observed, the other failures that were observed, in fact, in the Kaiser trial, and if you develop such a combined endpoint, the package together would let you address this issue.

ACTING CHAIRMAN DAUM: But that's not the question.

DR. GOLDBERG: It would need direct support. I think it depends on how you define your endpoints in however you define the otitis media trial

ACTING CHAIRMAN DAUM: Let me pose a question to you.

DR. GOLDBERG: Okay.

ACTING CHAIRMAN DAUM: Maybe this will help. If a trial is done and shows protection -- let's leave the number out.

DR. GOLDBERG: For otitis media?

ACTING CHAIRMAN DAUM: Against otitis. Would you agree or disagree that you could now --

DR. GOLDBERG: It would provide very strong support.

ACTING CHAIRMAN DAUM: Would you agree that it protected against invasive disease based just on those data or --

DR. GOLDBERG: Not necessarily.

ACTING CHAIRMAN DAUM: Okay.

DR. GOLDBERG: It probably wouldn't be large enough.

ACTING CHAIRMAN DAUM: We need that answer from you for this question. thank you.

Dr. Insel.

DR. INSEL: I have mixed feelings. On one hand, I can take the Giebink and Sam Katz model. You need more antibody in there. You've raised the bar higher, and if you can protect against otitis, that's great. It's likely then you'll protect against invasive disease, which would require less antibody.

On the other hand, I'm not sure if it's the same type of organisms that cause otitis media that cause invasive disease. That is, is it the organisms that have the ability to colonize for long periods of time that then you develop a viral otitis that then causes secondary bacterial otitis versus the organisms that you become exposed to and invade without even a period of colonization because they're different? They have differences.

And would this translate even into differences as far as capsular polysaccharide expression on their surface, susceptibility to opsonic antibody?

So from the standpoint of pathogenesis, I just throw that back out. I'd like to know a little bit more about the strings that are causing otitis media versus invasive disease, and how often do you see invasive disease occurring even after otitis and vice versa?

ACTING CHAIRMAN DAUM: Dr. Insel, I think you raised some very important points. I'd like to hear from the rest of the group.

DR. BUTLER: I would say no basically for the same reason. I think epidemiologically otitis media and invasive pneumococcal disease are distinct entities that just cannot be viewed as part of one spectrum.

Additionally, I find Dr. Giebink's data very interesting. I guess I'm still not convinced that the mechanisms of protection are similar enough to be comfortable with that either; that the role of mucosal immunity may be significant.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Hall.

DR. HALL: I would agree that overall I would not accept it as efficacy against invasive pneumococcal. The antibody being higher is a good

argument that it may be, but we don't know that, but the variability is too great with otitis media for, as mentioned before, local and other factors.

I did wonder though. It hasn't really been brought up, but I would accept more, say, the efficacy against pneumonia if that could be done, which brings up the question of the technical aspect of diagnosing pneumonia in this age group.

But if these tests were available or being worked on, then that may be another consideration.

ACTING CHAIRMAN DAUM: And Dr. McInnes.

DR. McINNES: I have nothing to add to my three learned colleagues on this side of the table.

ACTING CHAIRMAN DAUM: Thank you.

Not least.

DR. DECKER: I consider this question largely moot. If we said previously that you can license a seven-valent analogous to Prevnar on the basis of comparable immunogenicity however defined, and if you can license additional serotypes based on comparable immunogenicity however defined, then it's hard to imagine a study design that will get you to those points, that will get you to this without having gotten you to those points.

So the only issue, the only circumstances

where this question remains relevant is where you have a vaccine that is protective without being comparably immunogenic, the situation we discussed a little earlier.

So that is a very small area where you're now applying this. In that circumstance, then I would have to say no. The demonstration, as my colleagues have already said, the demonstration of efficacy -- you can't demonstrate comparable immunogenicity and all you can show is efficacy against otitis. Then you haven't crossed a high enough bar.

ACTING CHAIRMAN DAUM: Thank you very much.

I will make the last comment, and that is that mootness of the question aside, I agree with what most people are saying, that this bridge cannot be made yet between otitis media efficacy and invasive disease.

I must say that I'm very struck by the trial done in Finland and the one done in Northern California. If you really look at the vaccine serotype otitis, the numbers are the same. I think they're trying to tell us a true thing about the ability of the current version of Prevnar and its ability to prevent otitis media caused by serotypes in

the vaccine strain.

I think it's true. Why is it only 50 percent though? I've heard some ideas, but I don't think we really know why it's only 50 percent, and in part it's because we don't know the mechanism of protection by antibody against otitis media. There's lots and lots of missing information.

Having the sera that Dr. Siber told us will come soon from the failure patients may provide a clue. Looking at issues like the overall disease burden where in Finland it wasn't dramatically reduced as one might hope despite the 50 percent efficacy is another issue.

Does serotype replacement or some other kind of replacement fill in for the otitis media that the child is going to get anyway if we interfere with his pharyngeal carriage by having high titer vaccine?

Lots of questions here, and not a lot of light. I'm not ready to make this leap yet. I need a lot more information.

Someone, Dr. Hall I think, raised the question about a pneumonia study, and I think there are some issues there as well, as to whether the pneumonia can be read off the invasive disease model, but I'd feel a lot more comfortable trying to make

that leap than I would from the middle ear to the blood stream.

You know, if we prevent bacteremia, we expect to see the incidence of invasive disease go down, and if we prevent otitis media due to serotypes that are in the vaccine, we may or may not see the disease burden go down, and I think there's a lot more to understand here about pathogenesis and protection.

So I would not be comfortable making this bridge, and that's that.

We're at the close of our business today, which is good news for people with airplanes to make, but the committee will, of course, be trotted out one more time tomorrow morning for a final session. We will work through as efficiently as we can, but we will start at eight o'clock.

Thank you, and we need everybody here until the end because if there's no quorum, we can't do our business. So please don't go. Come tomorrow.

(Whereupon, at 4:14 p.m., the Advisory Committee meeting was adjourned, to reconvene at 8:00 a.m., Friday, March 9, 2001.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/PHS/CBER

Date: March 8, 2001

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.