reliably tell whether effectiveness will be changed by whether or not there are unacceptable levels of differences in this percent of people who achieve .15. I mean that's essentially the question on the floor.

So when Dr. Horne gave her elegant presentation, I agree with all of the mathematics. I think she's laid out the equivalence or non-inferiority trials arguments exactly correctly.

The complication here is two of the most complicated issues I've encountered in statistics are the issues of equivalence trial or non-inferiority, and the issue of surrogates, and we're putting them both together, and exactly as what she said.

What we're dealing with here is trying to define an acceptable difference on a surrogate so that we can say reliably that that's not leaving an unacceptable increase in the true clinical endpoint which is effectiveness.

So to move from there, using this simple example that I've talked about, we used to have 10,000 a year. Now we're down to 100 a year, 99 percent effectiveness. It seems to me there are from what I'm hearing today three ways in which we're moving from the 10,000 to the 100.

One of the ways is that we're decreasing

the organism carriage or what we call the pressure. I don't know how much of this effect is the pressure, but part of it is we're reducing the pressure with a vaccine strategy.

The other part is we're increasing the protection for the individual against susceptibility, and I'm going to guesstimate for sake of this discussion just to make the point that the pressure is one of the logs. It's going from 10,000 to 1,000, and I'm going to use as some justification as that the British data, which was basically showing that we had approximately a tenfold reduction in the presence of an active vaccine program for the risk amongst those people who were not vaccinated.

Now, you can get that data. I mean you can get some data on that to see if that projection is, in fact, proper.

Now, that means that if you were looking at unvaccinated people in a setting in which there's a vaccination program, those people are now at a risk of 1,000, not 10,000, but 1,000 per 100,000.

Now, amongst these people, there is going to be the risk that they have transmission before the age of six months, before the completion of three doses, and then those after, and what we had seen from

the original epidemiological data is that 15 percent of the risk occurs before six months and 85 percent of it occurs after.

So of these 1,000, you should have had 150 in an unvaccinated population of occurrence below six months and 850 after. What we're actually seeing in the CDC data that was presented here at the end is the actual number of cases in a vaccinated program is about a 50-50 split, which means that the focus here of all of the discussion has been on what is the percent of people who achieved this .15 once they've completed three doses, and the Reynolds and Zenco data are saying something pretty consistent to me. It's around 95 percent.

Well, that's very close to 50 over 850. That's in fact 94 percent protection in those infants who complete three doses.

The problem is the infants who didn't go through three doses either because there was noncompliance or that they weren't offered the three doses or because they became infected before they had a chance. There you're looking at relative to 150. So you have about a 67 percent protection.

Now, to come back to the specific quest

at hand here, what we're looking at in all of this discussion is only one of the three elements that leads to the 10,000 being reduced to the 100, which is specifically the element of what is the predicted level of protection in those infants that are fully vaccinated.

And what we're seeing is evidence that that is what is decreased from roughly 95 to 98 percent by five to ten percent less, and we're trying to use that as the basis to determine whether or not effectiveness is going to be reduced.

I would hope that it's also critical to look at whether or not the combination vaccines relative to the individual vaccines -- what's the relative immunogenicity in those who receive only two doses or one dose because in this setting, a lot of the risk occurs before six months, and in fact, it's my sense that when you look at the Alaskan data and you looked at the HbOC vaccine relative to the PRP-T vaccine, that the difference there between those two might substantially be -- the increased risk when you went from 30 back up to 60 might be occurring because of the lack of immunogenicity in those infants in less than six months, and this is really critical in a population such as the Alaska Native population where

25 percent, not 15, but 25 percent of the transmission is in that group.

So summarizing, this is clearly a correlate. Is it a surrogate? From my perspective we need to understand more clearly what level of -- to put it into Dr. Horne's presentation, as she clearly said, what is the null hypothesis, and if we're going to use this as our correlate, how much reduction can we allow in the percent to achieve .15 in order to run through this whole argument and say it's going to translate into an acceptable level of decreased effectiveness.

And my last comment is I don't think we've even answered that question yet, which is what do we believe, and maybe we'll come back to it. So I'll just lay it on the table.

We haven't answered to me the most important first question as to how much effectiveness are you willing to give up, and that's the first answer I need to have before I can even begin to answer how much immunogenicity will I give up.

CHAIRMAN GREENBERG: Well, I have assumed -- thank you very much, by the way. I think that that casts this discussion in a concrete and useful way. I just -- and I'm going to answer and this may cause

chaos here, but I had assumed that loss of -- that most people around this table were unwilling to lose almost any effectiveness. Now, I may be wrong here, and by almost any, I'll step out there: 25 more cases would be unacceptable.

So to go from 100 to 125, if you could really show that that was happening, would be -- around the table would be unacceptable. I'm making this up. Maybe you don't agree with me, but I would bet from a public standpoint that it would be pretty darn unacceptable to say children around the country are getting one less injection, but 25 more children are getting meningitis. That would be a tough one to sell.

PARTICIPANT: It's contrary to the 20-10 approach.

CHAIRMAN GREENBERG: So and I --

DR. SNIDER: Well, I think that's true, Harry, only to the extent that we can't answer your other important question about the benefits, and if we were able to show that we were going to prevent some of the other diseases that were in the combination vaccine --

CHAIRMAN GREENBERG: Absolutely.

DR. SNIDER: -- at a higher level, then

maybe we'd give up ten cases.

CHAIRMAN GREENBERG: One hundred percent correct, but --

DR. SNIDER: But for right now.

CHAIRMAN GREENBERG: Yeah, convenience, provider convenience would not be the rationale that would ever justify just that 25 percent, I don't think. Again, I'm just -- so as you think about this, I don't think anybody really has a lot of play in the decreased effectiveness in their minds.

I'm going to move on. Dr. Insel.

DR. INSEL: As has been said, antibody has been the gold standard, and I think it has to remain at least if not a gold standard at least a platinum standard or something of that order in the sense that in this instance we know antibody is the major effector function here. It's not just a correlate correlating with something else.

That having been said, then the question is how much antibody, and my bias is the more antibody, the better. I mean, we've heard that higher antibody is associated with decrease in carriage rates. Higher antibody levels are associated with better evidence of priming or memory.

So in general, I think, the more antibody

one is reassured. I guess the issues is if one were to give up antibody, then what do you have and can you depend on, let's say, memory, and there may problem is I don't know what the incubation period of this disease is. I do not know what the role of memory is as far as preventing disease.

In addition, the way we're looking at memory as has been pointed out, it's somewhat artificial. We're asking for challenging with a parenteral immunization to try to gauge what would happen with an infection that would occur, you know, at a mucosal surface.

In addition, we're challenging with a very high dose of antigen. I'm not sure we know everything about memory. I'm concerned even does the low level with the third dose in the first year of life in the primary series, does that reflect a low memory response that was induced by the second dose, and we know, for example, if we challenged between six and ten -- seven and ten months of age with polysaccharide vaccine that one would have a good memory response.

I'm worried about in that time period are we seeing, let's say, a reversal of some kind of effect and now memory is restored and looks very nice beginning at ten and popping in at 12 months of age.

What do we really know in that six to ten month window?

I raise it because of this question of, you know, reversibility of some of the effects that are seen with high dose protein.

So in the absence of really understanding memory, I think one is force to live with antibody, and then the question is: what are the relevant levels, and there I think it's very difficult to know.

CHAIRMAN GREENBERG: Thank you.

I'm now going to go to our guests and the same thing. Dr. Robbins would have been sitting over there. So I'll start with you. Do you have anything to add here, John?

DR. ROBBINS: It's not perfect, but it seems to be useful. It' the only thing we have.

CHAIRMAN GREENBERG: Dr. Heath.

DR. HEATH: Well, I would agree on the .15, but can I just add a little more data? Is that permissible at this point? Because a number of people have been asking questions about acute antibody.

CHAIRMAN GREENBERG: If you're going to help us with these questions, you should add.

DR. HEATH: I think it might help in that in our vaccine failures in the United Kingdom we've

been obtaining as best we can acute sera and also convalescent sera, and in about a quarter of the cases we have been able to obtain acute serum defined as within 48 hours of hospital admission, and the great majority of those children have very low antibody concentrations, as you would expect. Ninety percent of them are less than one, and about 50 percent undetectable, less than .15.

About two thirds have a convalescent antibody response which is acceptable, that is, two to three weeks after hospital admission their antibody concentrations are certainly greater than one, but one third have undetectable or very poor convalescent antibody responses.

So that I think help ones or two of the questions.

CHAIRMAN GREENBERG: Thank you.

Dr. McVernon.

DR. McVERNON: I'm very new to this area, but my perception is that as in everything in pediatrics, the development of immunity and even to a specific vaccine is a very age dependent phenomenon, and we know that avidity changes over time. I suspect that base elevation thresholds change over time, and certainly we know that in Alaska very high levels of

antibody required to protect the youngest infants, and I would say that, you know, antibody levels are the best thing we have at the moment, but I'm sure that it is an age dependent phenomenon and that different levels will be required at different ages for protection until we understand the mechanism more.

CHAIRMAN GREENBERG: Dr. Levine.

DR. LEVINE: I think my comments would parallel those that Kathy Edwards made. I guess I feel like we've been presented with data to make me feel like if we measure a kid who's received Hib conjugate vaccine and they have antibody levels somewhere between .15 and 1.0, that they're likely to be protected, they themselves, against invasive disease, and that doesn't speak to protection against colonization or other outcomes.

On the other hand, I guess one of the issues that you have to grapple with is even if you could come up with a very precise measure from a regulatory standpoint, how close would you want to be cutting it that way?

And I think one of the things about the 1.0 threshold, however arbitrary it may be and based on PRP plain polysaccharide, is that it gives you a little bit of a comfort area, and I think one of the

threads that I saw today was a degree of variability between studies, between populations, between areas, and one of the issues that concerns me is an issue of equity, and that is to say that, you know, if there are subpopulations of a high risk group that don't respond very well, I think we ought to not compromise their protection to make it more convenient for low risk populations.

And so although I think data was presented to suggest that you could ease off on the 1.0 micrograms, I would just want to try and balance that with the degree of comfort that we have in the absence of other measures.

CHAIRMAN GREENBERG: Dr. Steinhoff.

DR. STEINHOFF: I guess like everyone else I'll agree that these two threshold levels -- we have nothing else -- we have it to go on right now. I think so we've answered your question. These seem okay.

The question you didn't ask, however, though it's come up a number of times now is with what degree of stringency are we going to use these thresholds for new products. Must they be above must the mean titre be above 0.15? What about the titre of one for a new product, and is it after the

third dose and so forth?

So that we're not answering, but I think that's where the crucial issue is. It's come up a number of times, and I guess I'm the last one unless someone else is missing here.

So I don't know how that's dealt with.

CHAIRMAN GREENBERG: No, I'm the last one.

DR. STEINHOFF: Okay. You're the last one. I think these are appropriate thresholds. We've used them. The question is how are they to be used especially with new products.

CHAIRMAN GREENBERG: Okay. I'd like to -- I'm sorry. What did you say? Ah, excuse me. There's another panelist over here. Dr. Stein.

DR. STEIN: I think I also lean toward Dr. Edwards' point of view., I think we'll get into the discussion of immunologic memory later, and I might have more to say then.

CHAIRMAN GREENBERG: Okay, and for the record, I agree with everything that has been said.

(Laughter.)

CHAIRMAN GREENBERG: The only piece I might add is at least thinking about this in my mind, we've -- the other way to go, of course, is to say why are we -- why do we need to accept a decrease?

immunogenicity, especially when we have something set up like here? Why not say make combinations where immunogenicity is not sacrificed. It doesn't seem to me to be a first law of nature that immunogenicity has to be sacrificed with combinations. We've heard several.

And so while, for sure, from the manufacturer's standpoint when mixing thing that are already made together, there is decreased immunogenicity means more expense or extra work, it should not mean not going that route, and another way to approach this would be simply to devise strategies where immunogenicity had no change or was even enhanced in the combination.

And I would just encourage people to think about ways of doing it. I was struck by Dr. -- somebody said here simply, and I wonder whether maybe the manufacturers that tried it, simply a double barrelled syringe where mixture occurred only at the very last minute and wondered whether if alum is actually a major part in the amount of time that alum and the PRP are next to one another is critical, that might make a difference.

Has that experiment been done? It's like epoxy. When you --

PARTICIPANT: It works.

DR. EGAN: That's the next question.

CHAIRMAN GREENBERG: Okay. Do you have something relevant to this question?

DR. EDWARDS: Sort of, but I guess everybody could finish and then I could ask this comment.

CHAIRMAN GREENBERG: Okay. We have some more.

Dr. Edwards.

DR. EDWARDS: Okay. Well, I think it's interesting if we see that the current burden of disease is generally in the kids less than six months of age, at least 50 percent of them. One could also ask are we going to tolerate that. I mean, first of all, are those children all Native Americans? And if they are then presumably giving them the OMP will give them a good rise and then they'll have antibody and then they'll be boosted and then they'll be fine.

But what if they aren't? Does that mean then that we're going to tolerate the 50 kids that get invasive disease because they don't make an antibody till six months of age and we need to give everybody OMP and then follow with other vaccines?

You know, I think that's sort of an

interesting piece of information also, and that's not the question, but --

CHAIRMAN GREENBERG: No, and a good question or a good point.

Dixie, did you raise your hand? Were you raising your hand?

DR. SNIDER: Well, I just wanted you to clarify the point you were making because I think Bud Anthony got up and made plea about comparisons with the single antigen or single component as compared to a combination, and I guess I wouldn't be inclined to say that the combination would have to get the same anti-PRP response as the single antigen would, as long as the response is acceptable, in the acceptable range.

CHAIRMAN GREENBERG: I'm in total agreement.

DR. SNIDER: All right.

CHAIRMAN GREENBERG: I'm in total agreement.

DR. SNIDER: That's a clarification.

CHAIRMAN GREENBERG: All I was saying is that the discussion doesn't have to happen if there's no change in combination, and there are scientific strategies that might.

DR. SNIDER: Okay.

DR. FLEMING: Just a real quick follow-up question. I believe there is strong consensus on the fact that the antibodies specifically using a measure such as the percent that achieve .15, that this is correlated with the goal here of achieving protection.

I think also it has been argued the strong biological basis for the mechanism through which that correlation arises; it's also been argued by several what else can we use. Ultimately I'm assuming to answer this question completely though we would need to suggest in what way we would use this correlate as a way of assessing efficacy.

And we're challenged right now in a case like this because we're definitely seeing lessened immunogenicity by the measure that we're suggesting we're going to use. And so what is the scientific justification we are going to put forward for how much less we will allow in a way to reliably tell us how much less effectiveness will, in fact, be incurred?

And I'm looking for that discussion at some point before we go.

CHAIRMAN GREENBERG: Well, you don't hear it by the end of four, I'll let you have 4(a).

Shall we move on?

DR. EGAN: This is the related part of this first question, namely, to discuss and comment on to the extent possible the clinical significance of the diminutions in antibody response that had been observed with some of the conjugate vaccines in combination versus singly administered.

CHAIRMAN GREENBERG: Well, in part this touches Tom's question because if there's no clinical significance then -- so I'll just keep picking up the same person until I'm told to stop.

Dixie, do you have any feeling about this one?

DR. SNIDER: Well, the diminished immune responses with the combinations as compared to the single antigen or monovalent vaccine, I think it is a mixed bag. I mean, there's no way to answer that in a very general way. It's specific to, as far as I'm concerned, specific to specific vaccines, and in many cases I would submit that at least based on the immune correlates that we have, which we hope are surrogates there probably is no clinical significance.

But at some point somewhere along the way, there may be, and I think what we were saying earlier is that we don't know whether we'll hit that point anywhere along the way or not.

If we stay with the criteria we were just discussing, I think it's unlikely that we're going to get into clinical difficulty, although people were indicating that perhaps we shouldn't be too stringent in applying the .15 and the one.

Other people spoke in favor of being pretty stringent, and the degree to which you are less stringent, the more risk, I think, we run that there may be some clinically significant diminution in, I mean, responses.

I think the diminished immune responses that have been seen over time are also interesting and play into this, and I have no clue as to what that means. I hope that's a good sign in the sense that perhaps the population in general is not encountering the organism as frequently as it once did, and consequently is not getting boosted, and hopefully the lack of that boosting though doesn't lead to any increased immunologic susceptibility to infection or inability to rapidly mount a response to prevent invasive disease.

But I really don't know. Those are just some random reflections about a question I don't know the answer to.

DR. GRIFFIN: I think the only way we're

going to know about clinical significance is by following the population in the way that was done in Alaska, and because we have two levels of clinical significance, once is decrease in carriage rate and the other is protecting the individual, and so it's going to be a population based indicator when the clinical significance is diminished and Alaska, I think, is a wake-up or an indicator that it may occur.

CHAIRMAN GREENBERG: Thank you.

Dr. Stephens.

DR. STEPHENS: I agree. I think the Alaskan data suggesting that there may be increased risk associated with high rates of carriage is disturbing, and we need to keep that in mind, again, given the issue of effectiveness versus efficacy, which is an important discussion point.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I agree. I think the concern is whether we're now altering herd immunity, which hasn't been said, so I'll just mention that word again, and that's affecting then the carriage rates, and I think that needs to be monitored.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Well, I don't think we have a way of answering the question directly about combo

vaccines, but we do have a couple of canaries in the coal mine. One of them has been the Alaskan experience, which is very startling, and the other experience has been the PRP-D in the Native Americans, which is equally startling, and I'm surprised we hadn't spent a little more time talking about that.

But given our population which is so different than Finland or even than Germany, it's such a heterogeneous population, clearly there are pockets of very high risk kids, and I doubt that they're just limited to Native Americans in Alaska and on Indian reservations.

And in Question 3 I think we're going to spend some more time on those less than six month olds or less than seven month olds. It seems to me the more stringent we are right now until we know more, the safer we're going to be.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: Well, I'm not sure I'll be able to answer this question because I think question is somewhat generic. You said that immune responses are diminished, but the question is: how much, in what ways?

And the quality and quantity will be important, and without qualifying those issues,

generally I cannot say that it will be significant or not. I think that's, you know, my limitation in providing any information to this question.

But, again, as others have said, that in high risk populations, we have seen that considerable diminution of antibody responses have clinical consequences. So I think we need to bear that in mind.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: Yeah, I agree it is very difficult to assess the clinical significance of the diminished response, especially in the absence of comprehensive studies, as has been mentioned before, in high risk populations to include the urban Native Americans and inner city at risk.

We don't want to really take a chance of increasing disparity between a high risk and general population. I think it's another case in point for Rob Breiman's research subgroup from this committee, that we need to really take a hard look at this before we know the clinical significance of it.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: I would agree. The clinical significance of the diminished Hib immune response is that we have to find out why it's happening and what

kinds of kids it's happening.

Again, going back to find out the biological mechanism of the vaccine induced immune response, and I think paying more attention to individual differences between children before we assume that we can combine Hib with many other vaccines and not affect the incidence of Hib disease in this country.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I think the evidence that we've been shown about a lack of clinical significance in the use of the combination vaccines in Europe is encouraging. However, we are more heterogeneous in our population, and I think that that surveillance and actually the ABC surveillance system is very good, but I think surveillance does need to include a mandate that all Haemophilus will be typed from invasive sites.

And secondly, that we follow the experience of our colleagues in the U.K. where the vaccine failures are clearly looked at in terms of whether they are immune deficient in some way, whether they will go on to make an antibody response, and to characterize what the difficulties are.

CHAIRMAN GREENBERG: Dr. Breiman.

DR. BREIMAN: Again, similar to Kathy, I think that the key may lie with post marketing surveillance, and again, I'm impressed with the fact that we were presented today with two relevant non-parallel two relevant, parallel, yet not necessarily concordant sets of data. I mean one was the data from Germany which should have given us a fair bit of reassurance that you can get along with a combination vaccine, lower antibody levels and no apparent change in the rates.

And yet I think very disturbing data from Alaska that would suggest that at least in a high risk population there is a great deal of meaning in a reduction in immunogenicity.

So again, it highlights, you know, the need to look at various degrees of depth, carriage, and risk populations, and understand, you know, what the potential impact would be.

I mean one possible option, I guess, that hasn't even been discussed is if we knew more thoroughly what happened in Alaska, for instance, and what's going on in the Southwest among Apaches and Navajos. Is it reasonable to consider different targeted recommendations for vaccine use?

I mean, it may be that certain

subpopulations would need a, you know, separate injection and others would not. You know, I just don't think we're at the point yet that we understand enough about that.

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: Well, I concur. I think I at least am not at a point yet where I can understand fully the clinical significance of these --

PARTICIPANT: Can't hear you.

DR. EICKHOFF: -- of these decreases that we're seeing. Our surveillance system is certainly sensitive enough to pick up modest increases in cases which we haven't seen thus far.

On the other hand, the combination vaccines are not yet being widely used in the United States to my knowledge, at least. Please correct me if I'm wrong on that.

So I'm concerned about it as we move into the future, and I would be very reluctant to give up any of the clinical efficacy that we obviously have with this vaccine.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: I'd like to expand on a point regarding the Alaskan data and think that following the population both by culture and the pre-

immunization antibody titres would be very interesting to see if the background noise now is stimulating infants so that we will now have a new cycle in the curve where they will be more hyper responding than they have in the past.

That's one point I'd like to make, and then the second point is my concern about the very young infants who are constituting most of the failures now, and I wonder if anyone has data on antibodies in their mothers.

And I'm concerned about the antibody titres in young pregnant women and how that naturally then reflects on the vulnerability of the newborn babies within the first two months of life.

Many years ago at an army commission meeting, the late Dr. David Smith commented on data he had on pregnant women in South Carolina and how these were teenage women with very low antibody titres, and the vulnerability of their infants to Hib disease, and I don't know if anyone is tracking this, but we should have a very low antibody population now in the pregnancy prone group, and this may be accounting for some of the vulnerability in the very young babies.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: For me to provide an answer

of the clinical significance of the diminished Hib immune response, what I ideally would like to know is for this level of reduction in immune response, that translates into what level of increase in Hib cases, as commented in earlier discussion.

I realize that's an incredibly hard relationship to understand, but, again, in essence that's the relationship that is really driving the validity of this as a surrogate.

If I was to just throw out an approximation and use the concept of a threshold, just going back to what data we do have, if there were 10,000 cases a year and now there are 100 and half of those are occurring in those people that have had, infants that have had at least three doses, and that corresponds to about a 95 percent efficacy in that cohort, which also corresponds to Rennels' and Zenko's observation of the percent of infants that achieve the .15, if we interpreted that as being the threshold, i.e., you achieve that and you're protected; if you don't, then you don't, making that huge assumption, then observing in their data that we essentially double the fraction going from 95 to 90, the fraction of people who don't achieve that level, that threshold, that would translate into doubling the 50

cases to 100 in those that have been fully vaccinated, and those that haven't been would also correspondingly increase.

And then we have the issue as has been identified before. Then also what does it do to the herd immunity or the overall carriage, and that, too, is likely increased.

So that's how I would go about answering this, and I'm making a huge assumption about the threshold, but I'm awaiting another better way of answering the question, and until we get more data that really directly tells us what that functional relationship is, we're having to guess, but with the guesstimate I was using, it would exceed the number of additional cases that you had said before that you'd be willing to tolerate on an annual basis.

DR. INSEL: For the general population, I concur with what's been said. I think carriage and herd immunity there are the big issues for the high risk population. I think serum antibody may even be more important.

I just want to bring up another population, and that is patients with splenic dysfunction or splenia, such as Sickle Cell patients where having a preformed antibody on board at the time

of transmission or colonization would probably be very critical, and so there are other population groups that have been discussed heretofore that may be important as far as thinking how much antibody we want to have on board.

CHAIRMAN GREENBERG: Dr. Robbins.

DR. ROBBINS: I think the problem we have here is that the herd immunity conferred by mass immunization even with three injections in infants is protecting many more people than just vaccination alone.

Take a look at the example of diphtheria. Diphtheria vaccine where it's been studied is only 70 percent effective against preventing diphtheria. Half the people in the United States and almost all European countries have less than what the protective level, .01 international units per mL, has been measured. And it's possible to have protective levels of antibody and get diphtheria, but yet in our country we have none or one case per year, and that's because the organism has been virtually eliminated.

So from the point of vaccine regulation, it's very difficult to give numbers. What we do, of course, is to try to say that a new vaccine has to make at least two international units per mL after a

primary series, and that seems to be effective in the country.

Right now I would not like to give up one inch of efficacy that we've achieved so far with these Haemophilus vaccines, would not sacrifice any cases, and it appeals to me that about one month after the third injection of a primary series we should have something from 2.5 to three geometric mean titer.

The fourth injection probably solves our problem, but will not protect those very special populations that have the disease at a very early age, like Native American children in the southwestern United States and in Alaska.

It seems, I mean, if I had control of this, I would say that we mandate special consideration to use the optimum vaccination schedule today, which seems to be alternating the Merck product and the other two products to get the maximum antibody levels as early as possible in that population.

I think that technically the vaccines can be improved. The manufacturers, in general, have been reluctant to do this because of the enormous expense involved in doing a clinical study with five antigens on 100 infants.

And if government assistance is required

in this, I think this would be a reasonable request, and we have an administration that seems to be favorably disposed to assisting where assistance is needed.

DR. FLEMING: Harry, I'm sorry. Could I ask Dr. Robbins to expand slightly on his answer?

Given the premise that the major mechanism through which the current Hib vaccine has achieved production is through herd immunity to the level that's been achieved, how much reduction then can we allow in Hib immune response before it will affect the level of herd immunity that's been achieved?

DR. ROBBINS: Remember what happens. As soon as you start to vaccinate, the disease is depressed at all ages. In the U.K. it was reported to have a 50 percent reduction even before the children were immunized when that vaccine program started.

In Finland, you protected adults against epiglottitis. So it's very hard to measure that on a community basis, but for the moment, for the present, looking at the studies, and I don't have access to all of them -- CBER has to do this -- I would say I would not give up less than 2.5 to three micrograms of antibody one month after the primary series because with the fourth injection, you're going to do just

fine, but it's these very special populations for reasons that we don't understand that have the disease at a young age where we're not nearly as efficient as we could be in getting those last cases.

But I would have a number of -- I picked a number, 2.5 to three. Maybe CBER will do much better than I do, but I would not give up an inch on those. I would not go below those.

CHAIRMAN GREENBERG: Dr. Heath.

DR. HEATH: And I just agree that the clinical significance will depend on the population so that in Europe, well, in Germany, the United Kingdom and probably in the general U.S. population, the clinical significance would be very small, but in the Alaskan population it wold probably be very high and just support really the need for ongoing tight surveillance post implementation.

CHAIRMAN GREENBERG: Nothing to add?

Dr. Levine.

DR. LEVINE: Yeah, I guess that in following up to that comment, the issue is as Jay pointed out you have to have both increased susceptibility and continued transmission, and so that in environments like the U.S. where the general population in the U.S. where Hib colonization is quite

low, it may be quite a while before you saw any clinical significance of a change.

On the other hand, if the significance of that change is to create a cohort of children that aren't protecting against colonization, if there are reintroductions and then we reestablished transmission, you may then find the clinical significance appearing, and it's only through surveillance that we would be able to detect that.

CHAIRMAN GREENBERG: Dr. Snider. Hold on. Go on Dr. Steinhoff.

DR. STEINHOFF: Yeah, I agree with everything that's been said. I think I would urge that in the interest of simplifying the schedule reducing the shots and so forth, if you're considering adopting a combination vaccine, that's fine.

I would agree with what you said, Harry, that you're unwilling to give up even 25 cases. The point I would add to that is it seems likely that if we accept somewhat less immunogenicity and perhaps if perhaps a few more cases, we have to be careful that those cases are likely to appear in the high risk population so that they do need a special consideration either with a different schedule or with a different threshold.

We've heard a threshold now of two to three. Would that include 95 percent of the high risk population? I don't know.

So that I think this is a more detailed answer than we've been asked, but I'm unwilling to give up effectiveness, especially in populations that we know are at high risk. How this translates into policy I'm not sure.

CHAIRMAN GREENBERG: Dr. Stein.

DR. STEIN: I just want to correct for the record that I'm not an official member of the panel because I am an FDA employee, but I have been studying conjugate vaccines for over 20 years, and I think that that's the reason I'm here.

I don't want to add anything to the discussion on this point.

Thank you.

CHAIRMAN GREENBERG: And I agree with most of the comments that have been said. I guess the only other point I would raise is that if more and more vaccines are going to be added to these combinations, one might anticipate increasing opportunity for immunogenicity to be lost in the future so that holding immunogenicity at the present is not a bad idea because this same thing could happen the next

vaccine that you add.

And so it would be best to try to maintain immunogenicity.

DR. FLEMING: Can I just -- to reinforce that, following what you called immunogenicity -- what was your expression?

CHAIRMAN GREENBERG: Creep.

DR. FLEMING: Creep, and I used a different term. I called it the slippery slope in equivalence trials, the same exact concept. You do successive equivalence trials, and you can be increasingly ineffective.

If you use an adequately rigorous criterion for noninferiority, then generally your point estimate has to be the same or better to satisfy that criterion, and so if you're using standards that are rigorous, that is the best way to avoid the creep phenomenon.

MS. FISHER: I would like to ask Dr. Robbins one question.

CHAIRMAN GREENBERG: Okay.

MS. FISHER: Dr. Robbins, is it biologically possible for the Hib organism to mutate into a vaccine resistant form in the future?

DR. ROBBINS: Anything is possible. Is it

probable? I don't think so, but there have been very good studies from England with Haemophilus, and I'm not sure what lab it comes with, but meningococcus, but it might be capsule switching, might be, but is it probable? I doubt it.

Must we look for it? Of course.

DR. FERRIERI: I might add to that that the capsule switch has been well described in pneumococci and the antibody resistant pneumococci, and as Dr. Robbins says, it's been discussed regarding meningococcus C, and there's great concern in that in England where they've introduced the monovalent meningococcal C conjugate vaccine that they may, indeed, see a capsular switched with the other meningococcal serogroups.

CHAIRMAN GREENBERG: One second, Dr. Stephens.

Fortunately there is no time limit on this evening. So --

(Laughter.)

CHAIRMAN GREENBERG: So tomorrow, however, I am going to be a little bit more ruthless because I have to get home, but if any of you do have plans, I would again -- this is a very, very important problem, and we want to air it completely, but, again,

formulate your questions and be crisp.

Thank you, Dr. Stephens.

DR. STEPHENS: The issue of capsule switching, that was from a meningococcal standpoint an observation of our laboratory and also an in vivo observation from an outbreak occurring in the Pacific Northwest. So it does occur.

The question though with Hib is if you have capsule switching, are you switching to an, in essence, nonvirulent capsular type. In our surveillance project in Atlanta, which we've been doing for the last ten years or so, we've certainly not seen -- and I think this is CDC-wide as well -- we've not seen an increase in other capsular Haemophilus influenza types associated with disease.

DR. ROBBINS: Harry, just a point. The other capsule types by in vitro and animal assay are not virulent, and there's not a Haemophilus hole. If you close up the B, the others are not going to be virulent, but it is possible to make a super bug by putting another gene in and making three or four times as much capsule or to make an organism start shedding capsule very quickly, and that's why we must keep on looking.

Is it probable? I don't think so. Is it

possible? Anything is possible.

CHAIRMAN GREENBERG: Yeah. In biology that is clearly close to true.

DR. STEPHENS: Just as a comment, we've also looked at non-typable nasopharyngeal isolates to look for those organisms that, quote, might be turned off, if you will, in terms of B production, and we really don't find those, and that's another area of concern that has been raised regarding the vaccine.

DR. EGAN: And I guess one would have to worry about the acquisition of a non-Haemophilus caps in the title to Haemophilus (phonetic). Again, these are issues that we have touched on, but if you could please discuss the contribution to efficacy of immunologic memory, the demonstration of comparable functional antibody responses in comparing vaccines, and also the contribution to the eradication or diminution of carriage to the efficacy of the hidden conjugates.

DR. FERRIERI: Start on this side of the room.

CHAIRMAN GREENBERG: Okay. I was just going to see how long it would be before Dixie got mad.

(Laughter.)

DR. SNIDER: Well, I'm only going to be here about five more minutes. So --

CHAIRMAN GREENBERG: Okay. Dixie.

(Laughter.)

DR. SNIDER: So, you know, if you are going to let me have my say, I mean, clearly the answer to this would require that you line up the Hib conjugate vaccines and compare them head to head and see if the priming and functional antibody responses and eradication of carriage correlates with the other traditional measures of efficacy and the surrogate markers and so forth, and we don't have that kind of data.

So we don't -- and, in fact, what we have is a little bit confusing. For example, with regard to eradication of carriage, I would think based on what I've heard all day that that would be very important in trying to get this herd immunity that seems to be important for reducing Hib disease since we haven't been able to get 100 percent coverage in any population.

But yet what we saw from Alaska didn't really show a correlation between -- at least it appeared not to show a correlation between efficacy and preventing disease and efficacy and reduced

carriage.

Now, it may be that one has to take another stronger step in potency to be able to reduce carriage in that particular population with the vaccine or it may be that in that population it's not possible given all of the socioeconomic factors that are promoting the persistence of carriage. It may not be possible to do it with the vaccine. You just don't know.

But generally speaking, I would say that conjugate vaccines, any vaccine, but conjugate vaccines that reduced or eradicated carriage I would have greater confidence in.

I'll let other people speak to the immunologic issues and just briefly say that it seems to me that demonstration priming is important because this is an acute disease which can develop rather rapidly, and theoretically I would like -- would presume that having a number of primed memory cells around would be quite useful in preventing rapid onset of invasive disease.

And of course, with regard to functional antibodies, I would presume that the antibodies with greater avidity would be better than antibodies with lower avidity, and there already is some evidence that

isotype is important, and I think IgG-1, for example, is supposed to be important.

DR. EGAN: I think in part what was meant by this question, certainly elimination of carriage is the basis, you know, for the herd immunity, and it's quite important for that for, you know, children who are not immunized and for children who failed to respond, but is diminution or eradication of carriage important to the individual who's vaccinated? Is this another parameter that should be examined?

DR. FLEMING: Just from a mathematical modeling perspective, if we have a two log drop, which is essentially what the data are suggesting we have achieved with the current vaccination strategy, and if, in fact, -- and Dr. Robbins is claiming that it could be more than one of those two logs could be attributable to the pressure, the burden -- the benefit of that is not only in reducing risk to those who aren't vaccinated but those who are vaccinated have less baseline risk that you're trying to protect against. So it should matter for all of the patients.

DR. EGAN: That's what I wanted to include in this discussion.

MS. CHERRY: Dr. Edwards is filling in while Dr. Greenberg is out of the room.

DR. EDWARDS: Dixie, are you finished? No? Okay.

Diane.

DR. GRIFFIN: I think that priming has to be good, but I don't think priming or I didn't hear data that convinced me that priming was enough. I think that your most comfortable people have antibody on board at the time, at decent levels at the time that they're challenged with the organism. So I think that I wouldn't accept just evidence of priming as being indicative of the efficacy of the vaccine.

I mean obviously better antibody is probably better than bad antibody, but again, I didn't think we heard a lot of data on showing the different antibodies had remarkably different effects as far as predicting.

As far as eradication of carriage, for the individual, I mean, for many kinds of prophylaxis against disease, eradication of carriage actually is not something you achieve in the individual who is immunized often. It's more important for those around that individual for ability to spread that that individual be protected if they have adequate antibody to protect from invasion even if they continue to carry the organism.

DR. EDWARDS: David.

DR. STEPHENS: I don't have anything else to add. I agree with what's been said about Parts A and B. I again would emphasize the importance of eradication of carriage, and as a correlate of the effectiveness of this vaccine and one that has not been greatly emphasized in terms of data.

For example, this issue of three micrograms as being protective against carriage, as I understand it, is largely animal work, and there's really no good data that we've heard today about mucosal levels of antibody and the correlation with prevention of carriage, which I think is a very important issue.

DR. EDWARDS: Dr. Estes.

DR. ESTES: I don't have much to add. The issue of eradication of carriage in the individual to me, I agree with Diane that there are many vaccines that are effective in terms of the population where you're inducing herd immunity and you're lowering overall carriage, but I don't think that that has to be a factor for the efficacy of a particular vaccine in the individual.

DR. EDWARDS: Steve.

DR. KOHL: I would just urge that more

studies be done in these areas. Obviously, there is a fair bit of controversy, and we have a lot of smart people in the field. I think we ought to have some answers to this forthcoming, and I think animal models, as well as human studies will be helpful.

DR. EDWARDS: Dr. Kim.

DR. KIM: I agree with everything said about this topic. I guess I would add one more. That is, I think based on the cases, Haemophilus influenza Type B disease, it appears that preemies are increased risk. So with the patients, again, either they are fully immunized or partially immunized. Cases appear to be predominantly in preemies, and there are possibly issues related to A, B, and perhaps C.

So I would, you know, urge to include that population for studying these issues.

DR. EDWARDS: Dr. Faggett?

DR. FAGGETT: I agree with the previous speakers. I think this question though emphasizes the fact that we, as most of the speakers today, do really come to consensus that immunogenicity studies can be used in lieu of field efficacy trials.

That being said, I would like to see these areas really being looked at and more evidence base with the field trials and all of that. If you want

go with the immunogenicity studies, then it's even more important that these be looked at very seriously.

MS. FISHER: Yeah, I think we have to have more lab data before we get more clinical data, and I think that, you know, parents when they bring their child for vaccination and they accept the vaccine risk, a risk of a reaction, they assume efficacy. That's the reason they're doing it, so that their child is protected, and if there is any sacrifice, temporary or otherwise, in efficacy, I think parents are going to -- it's going to reflect poorly on the whole system, the whole vaccine system, and I think parents will come back for more shots if they are convinced that that vaccine is going to protect their child, as well as everything that is being done to limit vaccine reactions.

CHAIRMAN GREENBERG: Cathy?

DR. EDWARDS: I think Dr. Insel clearly showed us that the primary immune response and the memory response are closely linked. So I think that that suggests that a good vaccine that makes a good primary response is probably going to induce good memory, and again, it's hard to know exactly how quick memory can come and how many organisms you have and how quickly they invade.

But I think that is important. I think in general the avidity also shows that it does increase with vaccinations. In general the more immunogenic vaccines have the greater avidity. So those, again, are hand in hand and likely important in eradication, does certainly contribute to the importance of the efficacy of the vaccine.

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: Well, A, B, and C are almost surely important, and C may, in fact, turn out to be the most important. I will look forward to the day when some future Vaccines Advisory Committee probably at least a decade hence will be able to parse out the relative contribution to efficacy of those three components.

CHAIRMAN GREENBERG: Sage, sage words.

Dr. Ferrieri.

DR. FERRIERI: No words of wisdom, but I'd like to go on record as requesting more support from the federal agencies and more money for FDA and from NIH to support basic immunologic studies in this area. This is really critical.

I see ourselves all with gray hair coming back ten years from now. All of the new vaccines will create more complex issues for us, and so we're going

to continue to spin our wheels unless we very proactively dissect these issues out from the beginning, not at this stage after introduction.

I'm very supportive of post marketing studies, but also very proactive studies up front for any new vaccines that come along that we know are about ready to burst out.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: Well, I think from the perspective of immunogenicity looking at measures such as anti-PRP antibody levels and whether it's above .15, certainly that is an important correlate for susceptibility and carriage certainly should be anticipated to be an important measure of pressure or infectiousness.

My sense is from what I've heard, and for example, look at the Finnish data, and it appears that there's more going on than just specifically I call it accrued measure of percentage that achieved .15, and it's my sense that more fine tuning here, greater knowledge as we've indicated in Part B of functional antibody responses.

I guess ultimately what I would like to see is be able to get at is the most informed causal mechanism for reducing susceptibility in B and the

most specific causal mechanism for infectiousness when we're talking about carriage in C.

CHAIRMAN GREENBERG: Dr. Insel.

DR. INSEL: I don't think we've defined the role of memory and efficacy at this time. As I said, we don't know the incubation period for this disease.

I would challenge this group to think back to is there anything we can learn from epiglottitis in adults and why that was occurring in adults or some lesson to be learned from that. I don't have any answers, but it's something I've puzzled about some time.

Also it's important to point out as one gets older, even though antibody to the capsular polysaccharide is primarily the protective antibody here, one is making antibodies to other antigens on the surface of the bacteria that can also provide protection.

One quick comment on avidity. I just want to put it in perspective. When one immunizes with a protein antigen, we're talking about a change in avidity of three, even four logs. What we're talking about with a polysaccharide is very different. It's really fine tuning. It's usually less than a log.

And so as we measure this in vitro, and I think one can rig systems either based on bacteriocidal activity of opsonic activity to detect these differences, it a real question as to whether this is clinically meaningful. I just want to point out that this is true not just for this polysaccharide, but it's true for all polysaccharides. It's the nature of hydrophylicity and hydrophobicity (phonetic) if you can't raise it.

As far as isotype, I don't think we've seen any real differences here. IgG-1 and IgG-2, both can confer protection. I don't think that's a real problem

CHAIRMAN GREENBERG: Dr. Heath.

For the record, Dr. Heath has nothing to add.

Dr. Robbins. Same?

DR. ROBBINS: I agree with Dr. Eickhoff. I'm waiting to see how we can measure memory and how we can relate those two, but I'm patient.

CHAIRMAN GREENBERG: Dr. Levine.

DR. LEVINE: Yeah, I can't really comment beyond what's already been said on the priming and the functional antibody responses. In terms of the eradication of carriage or more properly protect-

against colonization, I think that we are at an issue -- we have an issue here where we don't have a good serologic correlate even close to what we have for protection against invasive disease, and I think that's a research gap.

Some people have pointed out that animal data suggests that it's two or three, and there haven't been human data. We did recently do an immunogenicity trial in Dominican Republic where Hib was not a routine vaccination, and there's still substantial Hib colonization. We vaccinated 600 children, bled them with three doses of PRP-T at ages two, four, and six months.

We bled them at seven months, measured their serum antibody levels and then collected NP swabs to look for Hib colonization at age nine months, and we found that although the GMCs in the overall population were over nine, all of the Hib colonized children had antibody levels at age seven months less than five micrograms, and the difference in protection between those less than five micrograms and those over five micrograms was quite significant.

I don't know if that means that five is your magic number, but I do think that what it suggests is that the threshold for protection against

colonization measured by serum antibody might be quite a bit higher than what it is for invasive disease, and that if you think about slipping, you know, your thresholds for what you consider an important threshold for vaccines, that may end up becoming a consequence of that.

DR. FERRIERI: May I ask Dr. Levine a question? Did you have any studies of nasal secretions to examine mucosal antibodies?

DR. LEVINE: No, we did not.

DR. FERRIERI: They're secreted antibodies.

DR. LEVINE: No, we did not.

CHAIRMAN GREENBERG: And Dr Robbins.

DR. ROBBINS: This has been well studied. Almost all of the antibody in almost all people that are in secretions in the respiratory tract are from the serum IgG. Conjugates do not induce secretory IgA antibodies to any degree. I mean you can't say no, but I think the level is so low and occurrence in individuals is so few I don't think it's important.

Serum IgG participates in mucosal immunity. I think I would not dwell on that too long. There's just no evidence that it has any participation.

CHAIRMAN GREENBERG: One moment Dr. Granoff.

We're polling the panelists now. Dr. Stein?

DR. STEIN: I just want to make a few quick observations. These conjugates work in infants because they shift the basic biology of the immune response from a thymus independent antigen to a thymus dependent response, and memory is an integral part of that, and what you normally see with a thymus dependent response, in addition to memory, is the generation of high affinity antibodies. These are usually accompanied by mutations in the antibody genes and selection for high affinity antibodies.

So I think memory is very important, and we've shown in our mouse models that when you prime with a conjugate vaccine, and we have a marker in the mouse for the T dependent response, that is, an IgG-1 antibody, you don't have this in humans. When you prime with a conjugate vaccine, the cells are switched to make IgG-1.

And when you transfer B cells from a primed animal into a naive recipient, you can boost the G-1 response with pure polysaccharide just as with conjugate.

So the cells are switched, and memory is an integral part of the biology of the thymus dependent conjugate vaccine.

In terms of the avidity, isotype and so on, when you measure the response to an antigen, you're looking at the combination of concentration and affinity, and unless you look specifically, you don't know whether you're seeing a little bit of high affinity antibody or a lot of low affinity antibody, and so I would encourage people to generate more data on the affinity in the antibody in various situations with single vaccines and combinations.

And I think Dick Insel had mentioned that the isotype, both G-1 and G-2 are protective, and I haven't seen any data that suggests there are major differences there, but I think we do need more data on the avidity.

I would also like to add for Dr. Ferrieri that through the generosity of the National Vaccine Program Office I am doing some studies on combination vaccines, and I will present some preliminary data next week at the combination vaccine meeting.

I hope that if we do establish a reproducible mouse model, and I think that's what's needed, then we can begin to answer the questions Dr

Fisher has asked at various meetings: what is the underlying mechanism by which we're getting protection with these vaccines?

And hopefully we will have that data. I agree we need more studies.

CHAIRMAN GREENBERG: We are maybe losing a few panelists. So I don't want to go a lot slower.

Dr. Granoff, I hope this is -- I want this pithy.

DR. GRANOFF: Pithy. But this is just a little history on --

CHAIRMAN GREENBERG: History is not pithy.

(Laughter.)

DR. GRANOFF: Well, no, because you this question is very germane to, I think, a quest... that I spent many years addressing, and that is ... plain Haemophilus poly saccharide vaccine story.

I mean after that vaccine was license... mean, I collected hundreds of cases of children ... were two to five years of age who developed inv... Haemophilus disease despite getting the p... polysaccharide, and within months after ... introduction of conjugate vaccines for the same ... the disease virtually disappeared, and it took ... years to get ten cases.

And if you asked the question what is the big difference between conjugate vaccine and plain polysaccharide, you remember we're looking at children two to five who are making pretty good antibody responses to the plain polysaccharide. What is the difference?

The conjugates give immunological memory. The conjugates give high avidity antibodies that are more functional. They give predominantly G-1, and they also affect carriage. So I think these factors are all very important in the effectiveness of conjugate vaccines that need to be taken into consideration.

Okay, and I actually agree with you. I think the key at least as a noninvestigator in this field is I'm not able to parse out which parts -- the conjugates do affect all of that -- but which are the operative modalities in decreasing rates in not clear to me, and yes, they affect carriage, and they affect isotype, and they affect isotype avidity, but I have not heard a lot of data that would enable anybody here to say it's equal parts of all of them; it's 99 parts/one, and that's what we need to know if we're going to move forward to know what part of the conjugate can't be sacrificed.

Okay. Number three.

PARTICIPANT: I thought we were --

CHAIRMAN GREENBERG: Oh, number four. No, we're on three. We're on three. We're on three. Wishful thinking, big guy.

DR. FAGGETT: Harry, can we possibly get CM credits for the day?

(Laughter.)

CHAIRMAN GREENBERG: You know, you've buttered your bread.

DR. EGAN: You get two for every hour past six.

There's a lot of historical data demonstrating variables in levels of serological responses with the currently licensed conjugate vaccines. How should we view or can we view, use this variability in considering the lowered immune responses that have been observed in the comparative trials.

And I guess we've seen some data from Dr. Granoff on some lowered responses with one vaccine. We've seen much data on variations between vaccines from four different vaccines.

CHAIRMAN GREENBERG: Diane?

DR. GRIFFIN: I thought maybe you were

going to start on the other end.

CHAIRMAN GREENBERG: I'm a righty.

DR. GRIFFIN: Well, I don't think I can really address this. I think in some ways it's a very interesting issue. I think in some ways it's a mathematical issue to try to figure out how these -- whether this variability all fits within a bigger picture of variability.

And I guess the only thing I would be concerned about is whether it's telling us something substantive about changes in the population perhaps or the fact that the organism isn't around so much and that you perhaps don't get as good an immune response, but basically I think it's a mathematical approach that I can't help with.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: I really don't have much to add to what's already been said because I think we've addressed a lot of this particular issue other than there may have been some clear effect upon the influence of the organism and its ability to induce priming or on cross-reactive organisms as has been mentioned earlier.

CHAIRMAN GREENBERG: Dr. Estes?

DR. ESTES: I have nothing to add.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: I think I've said what I can say.

CHAIRMAN GREENBERG: So you're seeing the panel tiring here.

(Laughter.)

CHAIRMAN GREENBERG: I knew we could wear them down eventually.

(Laughter.)

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: I think some may be real. Some may be mathematical as was said, but I think this issue has been -- questions have been raised in earlier discussions, is that some of the variability that we have seen we clearly do not understand the biologic basis for that. I think that, you know, is a big puzzle that certainly requires considerable investment in finding the answer.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: As a practicing primary care pediatrician, I have no comment on this question.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: I just think we should be concerned about the under six month age group and look at what other factors have changed in the past decade

that might be contributing, and I mentioned before Hepatitis B vaccine, and I still think we should look at that.

CHAIRMAN GREENBERG: Dr. Edwards?

DR. EDWARDS: There's been variability in interpretation of this assay from the time when I had black hair. It's been going on for at least two decades.

CHAIRMAN GREENBERG: And from the time when I had hair.

(Laughter.)

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: Only one thought to add. I think the decreased immunogenicity of the combination vaccines is real and something you need to pay attention to, and we are, rather than just part of the broad background of biological variability that we see with all vaccines.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: I feel we have said it all.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: Well, I'd say the goal is to sort out the signal from the noise, and both are impacting variability, both true effects that cause estimates to differ, as well as noise that can occur,

random variability, and my sense looking at all of this data is that there is clear signal that the Hib responses are lessened through combination vaccines even in the presence of the noise that exists.

The challenge was what we were discussing in the other questions. What caused the signal?

CHAIRMAN GREENBERG: Dr. Heath.

DR. HEATH: I have nothing to add.

CHAIRMAN GREENBERG: Dr. Robbins.

DR. ROBBINS: In a study in Chile the Haemophilus-tetanus conjugate was injected mixed with DTP and the aluminum where it projected separately, and three weeks after the third injection the difference between the groups were ten micrograms for the separate injection and three for the combined injection, but at 18 months there was no difference, and there were protective levels.

I think we have seen very few studies about the duration of vaccine induced antibodies. In fact, aside from the one that I put up with six years following an injection, there were none presented today; is that correct? Excuse me. I'm sorry.

I think that has to be done. If, indeed, a year or two after the primary injection there is no difference by injecting these combination vaccines,

then I think we can be more reassured.

I would also like to see what happens after the fourth injection, and I'll go back to the issue of the Native American children who suffer so much from this early onset disease that I think special consideration should be given to them.

I don't think you'll find any reluctance to try to set that up nor monies to finance it. People are interested in trying to see what we can do to protect, and I think the reluctance of some of those, of that population to give blood samples or to give other samples can be overcome if they can be convinced that what's being done is being done for their benefit.

CHAIRMAN GREENBERG: Dr. Levine.

DR. LEVINE: Nothing to add.

CHAIRMAN GREENBERG: Dr. Stein.

DR. STEIN: I agree with Dr. Robbins' comments. I think I would also like to know more about the cross-reacting antigens and the role in boosting. Certainly in the early days of evaluation of HbOC there were some children in the studies that appeared to have been self-boosted, and we don't know what antigen was doing that boosting.

So I would like to see some more studies

about environmental antigens that are cross-reacting and how that influences the level of antibody in conjugate immunized children.

I think in terms of the combination, you know, we are doing studies with combinations of Haemophilus DTaP and IPV in the lab which I will present next week. We are seeing some reductions in both Haemophilus and polio titres, and I think if we can, again, as I say, get a reproducible model we can begin to try to get at the mechanism.

As somebody who studied in red mice for many years, there are huge variations in individual titres in inbred mice, and if you don't have a control on levels in inbred mice, it's very hard to expect to have consistent levels in children.

So I think we need to get at the mechanism to be able to try to understand what's going on, and hopefully we will be able to do that in mice where we can do controlled experiments in large numbers of animals.

CHAIRMAN GREENBERG: Thank you, Dr. Stein.

For the record, I agree with most of the comments. I would like to say that I resonate most with Dr. Eickhoff and Dr. Fleming and simply state that the take-home message I'm getting here is that

there's a reduction in titre with combined vaccines, and it's there, and it's real, and I think we should not deal with this by saying it's okay, and therefore, we don't have to understand it.

It will eventually not be okay as you keep adding more and more combinations. We need to understand the mechanism, and I would assume that some of these mechanisms that are involved in decreased titre will have relevance to other combinations that are in the pipeline, and the sooner we figure it out the better.

Can I ask one question? For Native Americans -- this is a questions of ignorance -- is this true for a Native Americans or -- so in South America where the Indian population is huge, the Native American population is hugh. Haemophilus is a special problem?

DR. ROBBINS: There's a very good study by George Siber in which they injected the polysaccharide alone into I think it was Apache Indian children and Caucasian children in the area, and the difference between the two groups was statistically significant. It's one of the few genetic studies or population studies that show a real difference.

Actually the post immunization level

two year old Apache Indians was slightly lower than the pre-immunization level of the Caucasian children, but unfortunately they did not study Apache children who are living off the reservation.

CHAIRMAN GREENBERG: So I just wonder because there's such a large Native American population in South America, is Haemophilus a very big problem?

DR. ROBBINS: In Australia with Aboriginal people it's exactly the same thing. The attack rate of Haemophilus meningitis is about eight to ten times higher in Aboriginal children in Australia than it is in the Native population.

CHAIRMAN GREENBERG: Dr. Daum, we are -- no, we're moving on to the fourth question. We may get to it at the very end.

DR. EGAN: Okay. Again, we have touched on a lot of aspects of this, but the first part of this question is consider the relevance of the available post marketing data from Europe for the U.S. situation. So how do we interpret the U.K. data, the German data, other foreign data that may exist, and also if you can comment on the utility of epidemiologic surveillance systems and the use of them in studying the Haemophilus disease.

CHAIRMAN GREENBERG: I assume you're including the U.S. post marketing data.

DR. EGAN: Yes, the U.S. post market to this.

CHAIRMAN GREENBERG: Okay. Diane.

DR. GRIFFIN: I think the post marketing surveillance, certainly the epidemiologic surveillance is absolutely critical. I mean that's how various -- I mean it's how things were detected in Alaska as there being an upsurge in this disease.

I certainly think that we can pay attention to the European data, but I don't think we can use it for our population because it's just a more diverse population.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: I hope this is not implying that we endorse these combination vaccines and, therefore, will then study them in a post marketing kind of situation because I don't think any of us around this table, at least certainly not me, are endorsing that particular concept.

There are a number of very fine surveillance studies ongoing in this country as some of you know. The ABCs have been mentioned before. We, for example, began that, an active population

based study in 1988 for Haemophilus influenza B disease and have continued that for the last 12 years.

What we saw in adults was a decreased rate of Haemophilus influenza B disease. This was bacteremic disease associated with epiglottitis, associated with bacteremic pneumonia in adults in conjunction with the introduction of the conjugate vaccines.

That has remained. We virtually do not see in adults Haemophilus influenza B disease currently, and we're continuing that surveillance. I think this is true for the entire ABC surveillance nationwide.

So it certainly has had a major impact upon adult disease and continuing that kind of surveillance is obviously important for any of the vaccines that we're currently thinking about.

So those are two points.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I had just one other point to add. It sounded like the information from Canada might be interesting. We didn't hear a lot about that. The population there may be a little more similar to the population in the United States. That certainly should be considered.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: These kinds of studies are critical. I would urge that they be linked with better year 20 -- 2000 at least immunological data; that especially if we hook in with other societies, Pediatric Infectious Disease Society, the American Academy of Pediatrics.

The question was asked: how can we get samples on these kids? Most of these kids, I think, are taken care of in hospitals. Most of these kids are taken care of by, I hope, pediatric infectious disease consultation, and I think those samples, if it's made obvious that they're needed, will be forthcoming.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: Yeah, I concur with what Dr. Stephens said, that certainly I think that we are not discussing this issue, assuming that these products will be available to the public at this time, but again, with that in mind, I would concur with all the comments that have been made.

Certainly the experiences from other countries will be useful, but certainly would not substitute what is going on here.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: I would hope that the post marketing data would not only include efficacy but safety issues as well. I don't think we've really talked enough about that today, but here's one area. I think we should emphasize that as well.

CHAIRMAN GREENBERG: Ms. Fisher?

DR. EGAN: If I can just comment, I don't think we're -- you know, I think we're talking in the context of equivalent safety, not trading off safety for convenience.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: Yeah, and I think that's important when you're looking at combination vaccines, the safety factor, but in terms of the relevancy of the foreign data, I think it could be very important if the studies conducted in other countries would look at vaccine failures and do immune panels and do serological work to find out if there are genetic differences that could possibly apply to our country.

And, again, I also agree that we're not talking about post marketing surveillance in terms of assuming that we're going to combine these vaccines without further research.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I basically agree with all

that's been said. I think the only other thing that might be -- it's always controversial when you ask to collect DNA on anyone, but I think the vaccine failures, if possible, certainly we're going to have the genome soon, and if possible that might be something that could be looked at as well.

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: Really nothing to add.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: In earlier remarks I supported a number of these directions, and I would like to emphasize the importance of some of the genetic susceptibility, and we didn't touch on this because it relates to meningococcal disease, but a relatively good proportion of meningococcal disease may be related to a unique genetic susceptibility, and we don't understand this as well perhaps in some of the Haemophilus studies.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: I agree with the comments that have been made. It will be very enlightening to have careful surveillance, active and passive surveillance, in understanding and I agree the question does really directly suggest that the strategy will be licensed, and we're answering the

question in that context, and I share the concerns that have been expressed by others about whether that is the right step.

But assuming that that step were taken, it would be very important as many presenters have already acknowledged today to do this type of active and passive surveillance to understand, as I see it, all three components here we've been talking about. What is the effect of changing strategies here? What is the effect going to be over time on carriage and the pressure? What is the difference that will evolve in the actual level of protection in those who complete three doses, and what is the impact in those who, in fact, complete less than three?

To really best then use that data post marketing, if that's where we end up, then it would be best to have similar type of data pre-marketing to serve as the control. So I strongly endorse that we be attempting to get that information now.

I also acknowledge comments that others have said about the European data. It's certainly informative, but there are important differences that can exist in populations and in the vaccine schedules that might be delivered.

And, in fact, I haven't heard enough to be

as confident as we would need to be about the surveillance system in place there and how effective it is in capturing. If what we are talking about, as I have heard stated several times today, is sensitivities to small increased because even small increases would be unacceptable, is what I'm hearing today.

That means you have to have a surveillance system in place that is very sensitive, and I would need to know a lot more about the European systems that have been in place to know whether they would satisfy that criterion.

CHAIRMAN GREENBERG: Dr. Heath.

DR. HEATH: Well, perhaps we could talk more about the European surveillance system afterwards. Clearly we believe that post marketing surveillance is very important, and also not a particularly expensive tool to implement.

CHAIRMAN GREENBERG: Dr. Robbins.

DR. ROBBINS: Just one comment. The number of vaccine failures in the United States in children that have been fully vaccinated where we know the history are very few, very few. Most of the vaccine failures are due to incomplete vaccination or other things. I doubt very much if we're going

have any substantial information from attacking that problem.

It would be very difficult to get those samples, and you won't get many of them

CHAIRMAN GREENBERG: Dr. Levine.

DR. LEVINE: Thanks.

I think I would just echo the points that the surveillance is critical, and David Stephens pointed out that post marketing surveillance for invasive disease is good, but I also see us having some gaps here that there's incomplete surveillance for changes in susceptibility. Basically what I mean are changes in immunogenicity of vaccines as they are routinely used, and there's very little support for surveillance for colonization, and I think we're about to introduce pneumococcal conjugate vaccines and perhaps meningococcal vaccines, and maybe we ought to be thinking about this as a lesson in forethought for those.

CHAIRMAN GREENBERG: Dr. Stein.

DR. STEIN: It seems that I have the last work. I'd like to just thank everybody who's shared their data today. I think it's been a very helpful discussion.

CHAIRMAN GREENBERG: You don't have the

last work.

DR. STEIN: Oh.

(Laughter.)

CHAIRMAN GREENBERG: But thanking everybody --

DR. EGAN: This isn't even the last question.

CHAIRMAN GREENBERG: It's not even the last question.

So I have nothing to add to this surveillance. Post marketing surveillance is critical in almost all cases of vaccination and certainly in this case.

Now, there is a last question which is sort of an amazing question here. It's the stop gap question. It's have you missed anything.

DR. EGAN: Yeah, I mean this is where we make up for our -- this is where we at FDA make up for our ignorance and ask you where are we missing the point.

PARTICIPANT: Where are we missing the boat.

CHAIRMAN GREENBERG: So I have interrupted people along the way, and this is a chance.

DR. EGAN: But, yeah, but if -- Dr. Levine

just a little while ago presented some very, very interesting data about serum antibody levels and carriage from his study in the Dominican Republic, and I think if anybody else has additional data similar to that, it would be very nice to hear it as we cover this stop gap question.

CHAIRMAN GREENBERG: Can I ask a question about carriage, which was obviously very important and has been mentioned just in passing?

Am I correct that basically most of the data on measuring carrier state is simply a yes/no carrier state, not a quantitative carrier state?

And if that is the case, is quantitation important to this or is it the yes/no is all you need to know?

DR. FERRIERI: I think quantitation is important, and I did work with Haemophilus in rats, of course, years ago, and I think that it's not sufficient to have yes/no, but another technical point is the system you are using to assess colonization to be culture positive.

John, Dr. Robbins, may have a comment on this. I have a recollection that he had provided us with very potent antibody, and that you can incorporate it into auger and then look for halos

around the organism, and, John, is that a good way to be assessing carriage rather than just using, you know, a Haemophilus isolation auger?

Can you comment on that?

DR. ROBBINS: Just to set the record straight, that technique was discovered by Petri.

DR. FERRIERI: Oh, sorry.

(Laughter.)

DR. ROBBINS: And Margaret Pittman used it to standardize serum, but I think Orin Levine probably has had a lot of experience with using the technique in studying the problem. I wish he would comment on it.

DR. LEVINE: Well, we have consistently by the graciousness of the John used antiserum from his Burroughs pool to prepare the Hib antiserum agar plates. The quantification is difficult though.

There was a paper by Stonebreaker and Michaels in which they tried to quantitate that. I'm a little bit nervous about it, and I think while it would be nice, it's going to be very difficult. I would think it difficult to interpret those data.

When you put the goop on a plate, you know, we try to conserve the antiserum in the preparation of antiserum agar plates, and so we use

the smaller Petri dishes. It's very hard to get a spread so that you could actually count meaningful differences in the numbers of colonies.

CHAIRMAN GREENBERG: There's no quantitative PCR techniques that can now be brought to bear on this?

DR. LEVINE: I'm just an epidemiologist.

(Laughter.)

CHAIRMAN GREENBERG: I mean, are quantitative PCR is being used in microbiology all over the place. I would assume it would work just fine here if somebody would work it out.

DR. ROBBINS: There are differences in the infectivity of carriers, and that's been documented in many studies, including those done in Jamaica in the 1950s and '60s. I'll just tell you one.

Parents and siblings of children with meningitis invariably are colonized, but the parents and siblings of a carrier who's asymptomatic are rarely colonized. So there must be differences in infectivity.

I would think, Orin, that if you had a plate with one organism or two organisms as opposed to a confluent culture, you could give some guesstimate of how much is on the plate. It might be difficult

do in the interim, and you can use the large plates as long as the Burroughs syrup holds out, but unfortunately, poor Burrough 132 died after many years of service. He was 26 years old. That's an old monkey.

CHAIRMAN GREENBERG: Never had Haemophilus disease.

DR. ROBBINS: Well, we always thought Burrough 132 was a he until he had a child, and we thought that might be due to the Haemophilus, but --

(Laughter.)

CHAIRMAN GREENBERG: Are there other issues on the panel in the audience that you feel will be helpful to the FDA in dealing with this?

I'm looking. Do you see anybody? I'm missing -- ah.

DR. BOSLEGO: John Boslego, Merck.

I just wanted to amplify on some of the comments made by Dr. Granoff on the decline of HbOC over the years. We have not seen that with PRP-OMPC. It's been steady. The decade that we've looked at at the antibody response has been steady.

CHAIRMAN GREENBERG: So is this yet another difference in serology between studies?

DR. BOSLEGO: It's been very variable from

study to study.

CHAIRMAN GREENBERG: Dr. Fleming, did you have your hand up?

DR. FLEMING: Yeah. I think you promised me a 4(b) earlier on.

CHAIRMAN GREENBERG: I did. Good memory.

DR. FLEMING: And let me just reiterate what 4(b) was, and that was we gave essentially the majority of the panel gave an affirmative answer to 1(a), which was that the FDA currently using immunologic correlates of protection to assess efficacy was endorsed and, in fact, 1(a) was specifically referring to using serum antibody concentrations, i.e., anti-PRP levels above .15, and is this still appropriate to assess efficacy?

And my question was if, in fact, it is and the rationale as I recall for saying it was was based on biological arguments for why this could be the mechanism, although I've heard an awful lot of discussion about how this may be, in my words, a crude overall aspect of what the actual true mechanism is that might be fine tuned by understanding functional antibodies, et cetera, et cetera. What I haven't heard any discussion about is if it's going to be used as the way I would anticipate the FDA would use it as

has been outlined methodologically by Dr. Horne, one would need to define what level of difference you would allow in order to conclude that you have maintained efficacy at the level you wish to maintain it.

And this is really -- as I see it, the arguments for this has really been based more on the susceptibility issue. You're protecting an individual as opposed to what Dr. Robbins had pointed out might be the more influential mechanism of protection in the population for effectiveness, which is achieving reductions in the overall burden or pressure to the population.

And there, too, we've just heard something that certainly makes sense to me as well, if I'm quoting Dr. Robbins correctly, that there are differences in -- i.e., just that you're a carrier isn't, in essence, enough to know what the actual infectiousness is. So that, too, is in a sense a surrogate.

So if we are endorsing a positive answer to Question 1(a), which if you might not know I'll say directly I have a great reluctance of endorsing that because I don't know what the answer is as to what level of reduction you will allow in this proposed

surrogate as adequate evidence that you're maintaining efficacy or effectiveness.

CHAIRMAN GREENBERG: Well, I think, Tom, you're appropriately pushing people here, and does anybody -- does the FDA want to step up to the plate with this or does -- I don't the panel is exactly who would answer this. It's the FDA who's going to have to figure out are there any answers or is this --

DR. GOLDENTHAL: Well, this is Karen Goldenthal.

I don't think we have an answer to that, but I believe we've selected the delta ten percent as a way of asking the question of is there a difference. So, you know, selection of any particular delta has an element of arbitrariness, but that's the approach we've taken.

CHAIRMAN GREENBERG: I think that's as far as you're going to get.

Are there any other thoughts?

(No response.)

CHAIRMAN GREENBERG: Okay. Well, then I will adjourn this meeting. I want to remind you that tomorrow we start with an important disease, influenza at eight o'clock -- that was a joke -- and it's going to be -- as you recall, this is a very important

meeting tomorrow. I want you all to be here bright eyed and bushy tailed.

Oh, a couple of other announcements.

(Whereupon, at 6:48 p.m., the meeting was adjourned, to reconvene at 8:00 a.m., Friday, January 28, 2000.)

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: January 27, 2000

Place: Bethesda, MD

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