correct?

DR. FERRIERI: In the data that was distributed it was 0.15.

CHAIRMAN GREENBERG: Yeah.

DR. HEATH: And that's simply the graphs that were shown, simply comparing the clinical protection vaccine efficacy with the .15. It's simply just comparing the two.

Now, whether that's a valid thing to do, I think, is debatable. I'll leave that for you to decide, but it's simply based on the serological studies that I've showed you and the vaccine efficacy the clinical vaccine protection studies that I've showed you.

DR. FERRIERI: That was at the time of presentation with disease; is that correct? The serologic?

DR. HEATH: No, no. The serological data is from the studies of the persistence of antibody in a cohort of children who have been followed up since vaccination, primary vaccination.

DR. FERRIERI: Okay.

DR. HEATH: So clearly we're comparing two different groups, and apart from anything else, amongst the clinical vaccine failures, they will be a

different group. They're healthy children. In fact, about 30 percent of them have clinical risk factors for disease, such as immunosuppression.

A subset also have immunological deficiencies. So we're not comparing the same with same.

DR. FERRIERI: Thank you.

I wanted that teased out so that our memory is not just a straightforward take of that level and protection.

CHAIRMAN GREENBERG: Dr. Eickhoff, did you have a question?

DR. EICKHOFF: No.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: I also want to reemphasize what you said. Year one efficacy was approximately [illegible] percent, and then as you got further out it dropped a couple of percent, statistically significantly dropped.

DR. HEATH: Yes.

DR. KOHL: That's important that we keep in mind. If it's true what Dr. Siber said that [illegible] percent per year in this country is 90 more cases [illegible] H. flu disease, we're talking about a couple [illegible] hundred cases in this country if that data would hold

here.

CHAIRMAN GREENBERG: Dr. Breiman and then Dr. Fleming.

DR. BREIMAN: I also was looking at those numbers that you show for efficacy at 48 to 59 months and 60 to 71 months, and given the way you calculated it though based on the expected cases and the lower rates of disease, preexisting vaccine in those age groups and the likelihood that you'd always have a couple of escaped cases, people in whom the vaccine doesn't take, I don't know if you could get much of a higher efficacy rate the way you calculated it.

So I'm not sure if we can read so much into those differences because if you look at it, I mean, we're starting off at a much lower incidence rate pre-vaccination in those older kids. You know, how low can you go then when you only have a couple of cases in the vaccinated case?

DR. HEATH: Well, yes, I think you're right. I think that's a problem with this method, and as you say in the pre-vaccine era, the incidence of disease in the sixth year of life was very low. I certainly don't think we can go past that in our calculation. We can't look at the seventh and eighth years of life, for example.

But this is the way it was calculated. So particularly it's important, I think, in the first couple of years of life. It's harder to interpret as you go out.

CHAIRMAN GREENBERG: I have one more. Dr. Fleming, did you have a short question?

DR. FLEMING: Yeah, it really follows up on my earlier question. The data that you've clarified of the 14, 15 and ten for the year '95, six, and seven represent, in essence, the disease burden in a population in an era in which you have an effective vaccine, and so it's really one might say that the efficacy that you're computing as 99 percent could well be a combination of a reduction in the disease burden by a factor of ten as you go from the 108 to the ten to 15, and then, in turn, the reduction in susceptibility for those who are vaccinated by -- well, to get 99 percent efficacy by another factor of ten.

So that in essence, if you were doing a randomized comparative trial in the era of having the vaccine effect on disease burden already in place, then the vaccine is really giving you an additional 90 percent protection, another factor of ten, and so the correlate really would be giving you exactly what you

expect if it's predicting 90 percent rather than 99 percent.

DR. HEATH: Un-huh. I think that's fair.

CHAIRMAN GREENBERG: Last question, Dr. Levine if it's short.

DR. LEVINE: I'll try and make it very short. I'm just concerned that there's a little bit of discussion now that percentage changes like these are going to result in increased number of cases in the U.S., and that's I think going a little bit beyond the data here.

The fact of the matter is that many of the cases -- I don't know the data from the U.K., but I would suspect that many of the cases that are occurring right now in the era vaccination are the kind that Rob is describing, cases that don't respond to vaccine. They're very difficult to directly protect by the effects of vaccination. They are protected by herd immunity, and the fact is that in the absence of colonization, I'll bet I could go to Finland right now and substitute sterile saline for nine months and not have any breakthrough cases and come up with an efficacy of 100 percent.

So I don't think that this tradeoff of one percent back and forth is going to equal into 40 cases

just like that, and I'm concerned that we're making extrapolations that way that aren't founded.

CHAIRMAN GREENBERG: I have two thoughts before we move on, and just given our -- the United States potentially is a different population than both Germany and England, I would assume. At least we have Alaskan Natives in our population and perhaps other groups in greater numbers than Germany and England that might make direct comparisons of efficacy a little difficult.

But the question I want to ask for those of you involved in the immunology here, memory -- I'm having trouble with all of this memory stuff.

(Laughter.)

CHAIRMAN GREENBERG: Memory B cells, as I understand it, are small B cells that are floating around that have immunoglobulin on their surface and will bind the specific antigen and can be measured by flow methods now and quantitated very specifically rather than these -- no? I'm hearing no. It can't be done?

DR. INSEL: Memory B cells -- Insel, Rochester -- I'll talk about this in a few minutes, but memory B cells --

CHAIRMAN GREENBERG: Give your talk.

(Laughter.)

DR. EDWARDS: I think one question though that I'd like to make sure that we do hear before the day's over is the data from the CDC and particularly in what sort of vaccine failures. What's happening? Are they immunized or are they not immunized?

I know we've reviewed some of that, but I think there may be more information. So just --

CHAIRMAN GREENBERG: Well, we may be able to take that as we go over the questions.

DR. INSEL: Good. If I could have the first slide, please.

CHAIRMAN GREENBERG: Would you introduce yourself because I didn't do it?

DR. INSEL: Yeah. Insel, Rochester, New York.

I was asked to try to give an immunological explanation for the issue that is at hand, and what I'd like to do is really three parts of this talk.

First, I want to restate the question in immunological terms as your Chairman just started to do.

Second, I just want to give you some background and explain what memory B cells are and how

they're generated.

And, third, use that as a basis to try to explain to the best of my ability what may be going on here based on immunological principles.

So if I could have the first slide.

In a reductionist mode, I want to just reduce and compress everything you've heard into one, you know, sort of slide here.

First, with combination vaccines and comparison to immunization with separate vaccines, with the priming series in the first year of life we're seeing a decreased total, a decreased IgG antibody, and a decreased percent of children reaching a level of one microgram per mL or greater.

Second, not as severe a difference compared to separate immunizations, but if one compares children who have been primed with combination vaccines to separate priming, one finds also a decreased total in IgG antibody response to the booster dose. Although there's no question boosting is occurring, it is decreased in magnitude compared to children who have received separate immunizations.

The third point we've heard is that the ratio of IgG antibody to total antibody is not altered. We subclasses are not altered.

And last, that hasn't been discussed yet, but some studies have shown that the antibody to the carrier protein, whether it be tetanus or diphtheria toxoid, can also be decreased.

Well, taking that, I just want to reduce that to some terminology that I can at least talk about, and that is if you have a decreased antibody level, that means you have a decreased number of antibody secreting plasma cells that are secreting antibody to the polysaccharide.

Second, this decrease to the booster response as well as I'll contend that decreased response to the third dose in a priming series in the first year of life, I believe, reflects either a diminishment or a diminution in the number of memory B cells that are being generated and/or a decrease in their function, although obviously this is not as marked -- and we'll talk about this -- as the antibody secreting plasma cell defect that we've described this morning.

Now, what are plasma cells, what are memory cells, where are they generated, how can you identify them? A series of cartoons, Immunology 101. Very simple. Antigen introduced in the body ends up in secondary lymphoid tissues usually presented on the

surface of a dendritic cell to a naive T cell, at the same time presented to a B lymphocyte. The T lymphocyte can give both cognate cell-cell interactions as well as non-cognate interactions to that B cell through cytokines.

Initially what happens when that B cell is activated and activation is occurring in the secondary lymphoid organ and the extrafollicular region of lymph notes or the spleen, one of two things happens.

One, that B cell can generate what's called a short-lived plasma cell. That's a plasma cell that will form usually a foci in secondary lymphoid tissues called antibodies secreting cell foci. That cell can secrete, will secrete antibody. It's germ line encoded so that it's not going to have affinity maturation like we've heard about today, and it may or may not be isotype switched. It can be IGM or it can't through this T cell help, switched to IGG.

That's a short-lived cell that doesn't seem to stay around.

Now, the second thing that happens is that B cell, upon being activated, moves from the extrafollicular space to primary lymphoid follicles to form so-called secondary follicles with germinal centers. And what happens there is that B cell

undergoes up to 20 rounds of proliferation in this what's called the dark zone, and while it's proliferating the cell is undergoing hypermutation of its immunoglobulin variable region genes. These mutations are random.

That cell moves onward from this region into an area where it's no longer proliferating. It's called the light zone, and in that region, that cell which has then been mutated undergoes a process of selection, and that selection takes place with interactions with T cells, as well as with antigen to select those mutations that are expressed on the surface of that B cell, on the B cell receptor, those mutations that give rise to a better fitting antibody for antigen.

With that selection, you prevent cell death. That cell stays around, and then one of two things happen, and this is important to stress. We have two distinct pathways here which that B cell can go down, either to become a long-lived plasma cell or to become a memory B cell.

We know that these are distinct pathways. We know that the mechanism of their activation. The ligand receptor forms of interaction are very different. We know that the transcription factors

that activate cells along those two pathways are very different.

This plasma cell leaves the secondary lymphoid tissue, goes to the bone marrow, and resides in the bone marrow as a long-lived plasma cell. Obviously this plasma cell will have expressed antibodies that have mutated. So it's no longer germ line, and this explains some of the conversations this morning about affinity maturation because this cell now differs from that first plasma cell we saw because this has mutated antibodies.

How about the memory B cell? That memory B cell can continue to reside in this lymphoid organ or it can circulate elsewhere into the peripheral blood or to other secondary lymphoid organs or to the bone marrow. It can also go back and go back through this pathway, and this is a cell that can be restimulated upon reimmunization an regenerate this pathway and regenerate plasma cells.

We know that when you restimulate a memory B cell it looks like there's preferentially more differentiation toward the plasma cell pathway than back again to the memory B cell pathway, which would be beneficial in order to prevent, let's say, B cell clonal expansion and cancer, et cetera.

Now, one other point I want to make, and that is what we're talking about today, antibody responses to Haemophilus influenza B polysaccharide. This memory B cell has another characteristic. That memory B cell now can respond to unconjugated or isolated, purified polysaccharide. So it's matured to be able to respond to polysaccharide.

So having said that, how do conjugates really work, and what do we know about conjugates, and how can we use this to understand some of the interference that we may be seeing here?

First, I think it's important to consider what cell is presenting the conjugates to the immune system to T cell help, and one cell that we have to keep in mind what's very paramount here is the polysaccharide specific B cell. So this is a very simple cartoon. We've got a conjugate vaccine with a protein shown as a red square, a polysaccharide shown as a blue triangle, and this polysaccharide specific B -- polysaccharide conjugate can bind to this polysaccharide specific B cell through its B cell receptor. It will take up the conjugate, and it will cytose it. It will process this protein and represent peptides from this protein on its surface with MHC Class II molecules, which will then be presented to a

carrier protein specific T cell. That T cell then can direct help through cognate interactions directly at the B cell that's relevant for antibody formation to make an antibody to this polysaccharide.

Now, this is not the only cell that can present antigen, and I think it's important to remember that we have a set-up here for competition. What I've just showed you is here's our conjugate, and I just showed you it could be presented by this polysaccharide specific B cell.

Conversely, we have a carrier specific, in this case a tetanus specific B cell that can capture this antigen and to cytose it, process it, and present it to a T cell.

Furthermore, we've got dendritic cells that can capture this antigen. So one important point is we have a level of competition here as far as what binds the conjugate, and as I said, ideally what you want is this cell to capture the conjugate, direct T cell help to the polysaccharide specific B cell to drive it to proliferate and differentiate to become an antibody secreting cell.

The second point I want to make is that when these cells, these different cells take up antigen, they may process it differently. For

example, the way a dendritic cell or this B cell may see free tetanus may be different than when tetanus is conjugated to the polysaccharide because we know that glycoproteins can alter -- if you glycosylate a protein, it can alter its processing, and you can end up with different epitopes being presented by the antigen presenting cell.

The importance of that is that if you have primarily, let's say, dendritic cell processing and presentation, you may activate a T cell which may not be able to collaborate ideally with the epitope that's presented by this polysaccharide specific B cell. So there is a complexity here.

And the last general point I want to make is in general dendritic cells are probably very important for priming naive T cells, but once a naive T cell is primed and you have a memory T cell, antigen specific B cells -- B cells are very good at antigen presentation.

Well, having said that, where does the problem lie? Obviously if this was simple, we wouldn't be here. We'd all be home in the laboratory working on the next vaccine, but I believe that there are problems conceivably at several levels, and I want to walk through these.

I want to talk about alum. I want to talk about the dose of carrier protein, and I want to talk about pertussis. I want to talk about why antibody secreting cells are preferentially affected versus memory B cells, and I want to talk about why the Haemophilus antibody response is preferentially affected this way, and we'll go fairly quickly here.

First, I believe alum can be a major problem. As Dr. Robbins mentioned this morning, he and Dr. Schneerson and colleagues showed over 12 years ago that just adding a Haemophilus tetanus conjugate to aluminum hydroxide one had irreversible binding to the aluminum hydroxide complex.

Merck has shown that if one adds their PRP-OMP conjugate to aluminum hydroxide, that it's difficult to absorb the polysaccharide off the aluminum hydroxide, and this occurs in a very time dependent way. With time it's more and more difficult to chase off the polysaccharide off the alum.

Secondly, they showed that another effect was that there was hydrolysis of the phosphodiester bonds of the polysaccharide on the aluminum hydroxide backbone. What's the importance of this?

Well, what this means is one is going to have a decreased number of epitopes available to

challenge in the immune system, to capture that conjugate, and to present and act as a presenting cell. So this is one effect, and so in the schematic scheme of things, what you've have here is you'd have alum preventing this B cell from picking up this polysaccharide.

How can one get around this problem? Well, obviously double barrelled syringes may be an answer, and using aluminum phosphate as well as aluminum hydroxide may be a solution. So alum, I think, has to be looked at as one potential problem.

The second problem is how about the dose of carrier protein. I think there are two effects here. One is with a high dose of carrier protein we can get into problems, and there's another effect that I want to just discuss briefly called carrier induced epitopic suppression.

First, we know that if you give enough of any kind of protein, you'll create what's called high zone tolerance or high dose tolerance. This occurs probably because when you stimulate a T cell with antigen, that T cell must be simultaneously stimulated with co-stimulatory molecules. If there's excess antigen, you'll have that T cell being hit with the antigen in the absence of co-stimulatory molecules

and that will lead to either T cell anergy, immune deviation, or suppression.

And this phenomena, does it occur in man? This is an article published by Ron Dagan and Juhani Eskola where they immunized one limb with a pneumococcal-tetanus conjugate at increasing doses and another limb with Haemophilus tetanus at a constant dose. As they increased the dose of the pneumococcal-tetanus conjugate from 39 micrograms of tetanus to 111 micrograms of tetanus, what they saw was approximately threefold decrease in the amount of antibody to polysaccharide. Now, this was at a different site.

In addition, as they went up to 111 micrograms of tetanus, they began to see a significant decrease in the antibody response to tetanus. I interpret this as an example of too much protein can alter T cell responses and can, therefore, affect the response to any hapten or saccharide that is coupled to that protein carrier.

The second phenomenon that one has to deal with is this phenomenon called carrier induced epitopic suppression. This is originally described by Lee Hertzenberg as based on the concept that haptens which are coupled to a carrier, that antibody responses to those haptens are decreased if one pre-

immunizes with the carrier proteins.

What is the mechanism of that effect? We don't know for sure. Several mechanisms have been proposed and shown to be whole in animal models.

The first is that with high doses of protein carriers, one can increase the number of carrier specific B cells, and as I said, they can compete with hapten or polysaccharide specific B cells for capture of that conjugate and recruitment of T cell help.

Second, others have shown that you do generate memory B cells to the hapten, but that those B cells are unresponsive to T dependent antigens. They'll respond to TI antigens, but they fail to respond to TD antigens, and they will fail to make and differentiate to become antibody secreting cells in vitro.

It's of interest that this process appears to be reversible, and with time it looks like it can correct itself.

The third level at which CIES may be occurring is at the level of antigen presenting cells. It's been shown that if one presents antigen on the surface of dendritic cells, that one can overcome this, and thus, this may be an effect of the cytokine

milieux or the cell that ends up presenting high doses of carrier.

Schematically, in a cartoon fashion, here we have high dose carrier protein expanding the number, activating T cell help and expanding the number of carrier specific B cells, and what this will lead to is an expansion of these carrier specific B cells which will preferentially capture the conjugate. The conjugate won't be taken up as readily by the polysaccharide specific B cells, and thus, T cell help will be directed primarily at these B cells and not at polysaccharide specific B cells.

Similarly, the high dose of carrier may activate T cells that can't collaborate with the hapten, the epitope that's presented by these polysaccharide specific B cells.

And last, as I mentioned, it looks like there's a defect in this terminal differentiation of these cells that are generated with high dose carrier, and this may be because they're generated with insufficient T cell help and, thus, they don't respond very well as far as differentiating.

Next, what about pertussis. As we switch from whole cell pertussis to acellular pertussis, we have seen this problem. As this group knows, with

whole cell pertussis, we didn't have this problem. Why the difference?

Well, I think there's several possibilities. First, and these are really questions, is it possible that the presence of whole cell pertussis affects the interactions between the polysaccharide and the alum and can overcome that alum saccharide effect because there are lots of other components in whole cell pertussis that may be binding to aluminum hydroxide?

Is it possible that with whole cell pertussis we had an adjuvant, a nonspecific adjuvant effect on dendritic cells to overcome this effect?

Is it possible that as we switch from particulate whole cell pertussis to soluble acellular pertussis this has had an effect on antigen presenting cells?

We know that acellular pertussis -- that some of the vaccines do have an increased level of PT and FHA. Is that have an effect?

Vogel and colleagues showed quite a while ago, a decade or so ago, that you can overcome carrier induced epitopic suppression with pertussis LPS, and is it possible that the whole cell pertussis and its small amount of LPS component was altering an

abrogating the effects of CIES?

And last, is there some kind of effect on the dendritic cell as far as CIES -- sorry -- as far as the cytokines they produce?

So simply, whole cell pertussis may be blocking interaction between alum and polysaccharide, may be an effect on the dendritic cell through this adjuvant effect, altering it while H. cellular pertussis doesn't have this effect; overcoming the CIES effects through its LPS; or altering the cytokine milieux.

Obviously all questions really need to be further explored to really answer that.

CHAIRMAN GREENBERG: Richard, you've got about two more minutes.

DR. INSEL: Okay. In the last two minutes, how about why is antibody affected rather than memory B cells?

I would contend, as I told you, the activation requirements are quite different. It looks like that antibody secreting cells, activating them, that activation appears to be much more stringent than memory B cells, and there were hints of that in the past.

We saw from the Hib-OMP vaccine in the

Merck product that that vaccine was not very effective if one gave a third dose at six months of age as far as generating an antibody response, but yet that same vaccine, if used in the second year of life, was very good at reactivating an antibody response.

Some of the early experience with conjugate vaccine, the first vaccines that Porter Anderson made in Rochester, those vaccines were very poor at generating serum antibody, but very good at generating memory.

The work of Juhani Eskola showing that if you immunize neonates, neonates generate -- they can generate memory responses, but very poor serum antibody responses.

And then as I mentioned, memory B cells may not generate antibody secreting cells because of CIES.

Why Haemophilus? I think it's because what we've showed many years ago is that the clonal response to Haemophilus is extremely restrictive in diversity, a limited number of clonal type, a limited number of VG. So you've got low B cell numbers.

In addition, you've got this immaturity, and I think both of those are the reasons why this is affected.

So, in summary, I think alum, the carrier protein, the pertussis are all -- should be implicated, and I think the sensitivity of the antibody secreting side of things in Haemophilus explain why this has been picked out.

Thank you.

CHAIRMAN GREENBERG: Thank you for Immunology 101, humoral immunity.

We have a few minutes before the break. Do I have some questions?

That was very helpful. I still, if you don't mind, want to --

DR. INSEL: Yeah, I didn't answer your question, and your question was how you can identify memory --

CHAIRMAN GREENBERG: You started --

DR. INSEL: I know.

CHAIRMAN GREENBERG: -- and you defined two sets of cells, and nobody --

DR. INSEL: But I decided to --

CHAIRMAN GREENBERG: -- has really talked about --

DR. INSEL: But I decided I didn't was to use my time for your questions. So I'll do it now.

(Laughter.)

DR. INSEL: So the question that's on the table is: can one identify memory B cells? What is their phenotype? And more specifically, can one identify antigen specific memory B cells?

We define memory B cells. They do circulate. Memory B cells are defined as IgG negative, CD-27 positive B cells. They are in circulation, and they can represent approximately ten to 15 percent of B cells in their circulation.

Second level is can one define antigen specific memory B cells. It's extremely difficult, and where it has been done though is that people have been able to identify tetanus specific circulating memory B cells, and when they do this, it's very interesting because the level of those cells do not correlate with serum antibody to tetanus toxoid.

So we do have this dissociation between serum antibody levels and memory B cells, and I would say right now when we look at a serum antibody level, we don't know for sure how much of that is coming from long-lived plasma cells versus B cells that are continually -- memory B cells that are continuing to differentiate into plasma cells, and I could contend this is an area that really needs future investigation.

Can I just ask for my own benefit one further question? Those memory B cells could be identified by the fact that they have surface antigen specific immunoglobulin on their surface that can be identified by flow if you have labeled here a beautiful antigen. No?

DR. INSEL: The problem is, the problem is the precursor. The cell number is so low that it's extremely -- even with the tetanus the numbers we think would have a much higher frequency. It's extremely difficult to get at those. It's a good question, and it's a great goal, but I think right now it's extremely difficult even by facts.

CHAIRMAN GREENBERG: Dr. Snider.

DR. SNIDER: Yes. I wonder if you'd comment, please, on an issue that was raised early this morning, which was, as I recall, that infants are susceptible, but then at least in the past they've encountered not only Haemophilus influenza B, but they've encountered this polysaccharide or a very similar polysaccharide in E. coli and other organisms, and therefore, maintained to have been able to boost, presumably boost as a result of those kinds of exposures.

What is your view on that and how does

that also play into the scenario that we're thinking about today?

I think once one has generated a memory B cell for this polysaccharide, that cell can respond either to the isolated polysaccharide, to the polysaccharide presented on a different carrier, or a polysaccharide presented on either Haemophilus or another organism, such as E. coli, you know, K-100 or staphylococcus.

So that cell now can -- is seeing a particular saccharide. Now, obviously that's simplistic in the sense that we know that even for any given polysaccharide there are multiple epitopes, but as long as there's something cross-reactive between, let's say K-100 and the Haemophilus polysaccharide or between the ribitol-5 phosphate, staphylococcus, and Haemophilus influenza B, and you have a B cell specific for, let's say, that ribitol-5 B phosphate moiety. That cell could respond if it's been primed this way.

CHAIRMAN GREENBERG: A few more questions. Dr. Kohl.

DR. KOHL: Richard, could you please characterize stringently for us what priming to a polysaccharide looks like?

DR. INSEL: So the question is what does priming to a polysaccharide consist of? Obviously that's, you know, the big question. Really the question is now that you have, let's say, generated this memory B cell why can it respond to an isolated polysaccharide.

DR. KOHL: No, no.

DR. INSEL: Is that what you're asking?

DR. KOHL: How can we tell that priming is occurring?

DR. INSEL: Well, I think --

DR. KOHL: We've been given different definitions so far today.

DR. INSEL: Okay.

DR. KOHL: By magnitude, by kinetics, by isotype, et cetera. What would you define as the stringent criteria for priming?

DR. INSEL: My criteria would be that if a B cell can respond to the isolated polysaccharide, that B cell has been primed.

CHAIRMAN GREENBERG: By secretion of antibody?

DR. INSEL: By secretion of antibody.

CHAIRMAN GREENBERG: There's a question over here.

DR. STEIN: Dick, I actually had a two part question about environmental antigens.

CHAIRMAN GREENBERG: Could you identify?

DR. STEIN: Yes. Katy Stein, CBER.

About environmental antigens priming or boosting an immune system, Dr. Snider asked the first question. I guess the second question I have is: do you or does anybody else have data to indicate that widespread use of Haemophilus vaccines has decreased the population with cross-reacting antigens? For example, is there reduced colonization with E. coli K-100 in the gut as a result of immunity to Haemophilus?

DR. INSEL: I don't have that data. I would tend to doubt that that would ever be the case because as far as E. coli K-100 in the gut, because I can't believe you have enough antibody at that site to really have that effect, but maybe someone else could comment as far as colonization with cross-reactive antigens.

CHAIRMAN GREENBERG: Does anybody have the answer to that question?

Okay. No.

DR. GOLDBLATT: David Goldblatt, London.

I just wanted to address your question, the Chairman's question about why can't we just do a

bit of flow cytometry and find a memory B cell. And essentially I think a majority of us in the room believe that memory is important in some form or other in protection for Haemophilus, and we're all looking. This is the Holy Grail. We all want to look for a marker of memory.

But the problem is that the blood is really not the right compartment for memory because memory essentially for something like Haemophilus has to exist on mucosal surfaces, and we know that memory B cells will reside in the spleen, will reside in the bone marrow, and reside in the submucosae where they are essentially going to be in contact with the antigen first.

Because, of course, if the Haemophilus gets into the blood stream, that is a little late for your memory to kick in. So --

CHAIRMAN GREENBERG: I agree with you, except this memory is generated from a vaccine. The memory that is being generated here is not being generated by Mother Nature, and so perhaps that memory B cell hasn't been taught to reside at the mucosa.

DR. GOLDBLATT: Well, no, I think it has. I think it has, and if you have mice rather than children, then you can go and chop them up, and you

can find those memory B cells in the compartment that you expect them to.

Now, earlier on, we heard a little bit about avidity. Now unfortunately, the whole issue of avidity and affinity gets confused because we have one group of researcher who are looking at the correlation of avidity as a functional correlate. In other words, a lot of high avidity antibody versus low -- lots of low avidity versus small amounts of high avidity.

But the way that we've been using it in our laboratory, avidity, is as a surrogate marker of memory. In other words, look at the changes in avidity over time even though antibody is declining, and as a number of speakers have already alluded to, the phenomenon that is seen is an increase in avidity over time following conjugate priming.

That does not occur if you give a plain polysaccharide vaccine. That only occurs if you give a conjugate. So that perhaps is one of the surrogates we need to focus on as a surrogate of memory.

CHAIRMAN GREENBERG: I'm going to have one more question, and then we'll take a break. Is there another question?

Dr. Kim.

DR. KIM: I guess based on what you just

presented, can you speculate perhaps. The question which I raised early on is potential mechanism of IPV interference compared to OPV.

DR. INSEL: I don't have the answer. The only thing I could speculate on is whether through cytokine release it's altering presentation in some way in the cytokine milieux and possibly deviating from a TH-2 to a TH-1 type response, but I have absolutely no idea why IPV is doing that.

CHAIRMAN GREENBERG: We'll take a ten minute break, and so I would like everybody here -- actually it'll be a 12 minute break -- at 3:30 sharp.

(Whereupon, the foregoing matter went off the record at 3:19 p.m. and went back on the record at 3:34 p.m.)

CHAIRMAN GREENBERG: Okay. This has been a lot of data, and we have a little bit more data. I hope -- this has been a lot of data. I'm sort of bending under all the data.

The next talk is by Dr. Dale Horne from the FDA on trial design and analysis. Maybe that will put us out of our misery.

(Laughter.)

PARTICIPANT: Speak for yourself.

DR. HORNE: That's the first time I've

heard a statistics presentation being referred to as putting one out of one's misery.

I'm from CBER's Division of Biostatistics.

Office of Vaccines asked me to talk to you today about how we evaluate combination vaccines from the perspective of design and analysis. So you're going to be subjected to a 15 minute lecture on statistics, but I promise it will be painless, and I guarantee you'll all leave here today having understood everything I said.

When we were thinking about writing our guidance document on combination vaccines, we were wondering, you know, what are we going to do with these vaccine studies. How are we going to have them designed? How are we going to evaluate them?

So we looked at the Code of Federal Regulations for guidance because we are legally required to follow that. So this particular part of the CFR seemed to speak to us and tell us what we needed to know.

Clearly there is concern that combining different antigens into one injection should not create a product that is inferior with respect to any of the individual components.

Now, we know that because of inherent

biological variability we can't really show that two products are exactly identical, but we can show that they are similar within some specified margin.

So we translated that section of the CFR into meaning that the aim regarding effectiveness would be to demonstrate that combining antigens into a single injection does not reduce efficacy by a clinically meaningful amount for each vaccine component.

Thus, the concern was obviously one directional. There's no reason to limit superiority of the combination vaccine, and so it seemed clear to us that these trials should be designed as non-inferiority or one-sided equivalence trials.

Now, when we were writing the combination vaccine guidance document, the term "non-inferiority" was not in common use. So what we allude to in the guidance document is one-sided equivalence trials, but what we're talking about is non-inferiority.

The efficacy endpoints are usually not cases of disease, especially if the components are licensed or their efficacy has been previously demonstrated, and this is because disease incidence may be too low due to widespread use of the separate vaccine components in a population.

And so measures of immune response are used as correlates of protection, and these are not as easy to understand as clinical endpoints, and that may be the understatement of the year.

The immune response endpoints that we look at are geometric mean concentrations, and then proportions responding in a pre-specified manner. For example, for Hib, we look at post vaccine anti-PRP antibody concentration greater than or equal to .15 micrograms and also greater than or equal to one microgram.

Now, it's important if the desire is to make inferences from the results of this study rather than just generate hypotheses and do exploratory analyses. It's important to have hypotheses formally specified. We're accustomed to seeing the null hypothesis listed first and the alternative listed second beneath the null.

I have a preference for beginning with the alternative hypothesis.

Now, specifying hypotheses is unbelievably easy. It's very simple. A person doesn't have to be a statistician to write down hypotheses. Once you know what your primary endpoint is, just decide what is it that you want the trial to accomplish with

respect to that endpoint. That is your alternative hypothesis.

You can write that down in plain English or whatever language you prefer to use. Then your null is just everything else. It's that simple.

Then a statistician can take those statements and translate them into statistical statements.

An important point is to recognize that we design trials to reject, not demonstrate the null hypothesis. Now, that's a key point. That's the reason why we're not going to be specifying the usual, conventional null hypothesis of no difference because what we're doing here is a one-sided equivalence trial.

Now, a consequence, an important and nice consequence of specifying the hypotheses in the manner that I just showed you is that your error probabilities have the usual meaning. They haven't changed at all.

A lot of people had the mistaken notion that when you're doing an equivalence trial whether one sided or two sided, that your Type I and Type II errors get flipped around. That's not true at all.

If you think that's true, that's a pretty

clear sign that you've misspecified your hypotheses, and it's a pretty good sign you need to go back in and see what you need to do to change that.

So the Type I error alpha means what we're accustomed to it meaning. It's the probability of projecting the null when it is true or, in this particular case that we're interested in today, is claiming noninferiority when the combination is, in fact, inferior.

And then the Type II error means the usual thing. The probability of not rejecting the null when it has faults or in the case of non-inferiority trails of combination vaccines, it's failing to demonstrate non-inferiority when the combination is truly non-inferior.

Now, with respect to geometric mean concentrations, we can specify our hypotheses in this manner. The alternative suggests that we're interested in a quantity, in estimating a quantity theta, which is the ratio of the geometric meaning, the combination to the geometric meaning the separate, and we want to see if that ratio is greater than some pre-specified quantity theta naught.

Now, I said that specifying hypotheses is quite simple, and it is. The difficult part is

specifying that theta naught. Should it be .5, .66. I've seen both used. Perhaps it should be something else.

That's the difficult part, is determining what is clinically meaningful for these studies.

Now, note that the hypotheses that you just saw were statements about the ratio. We're interested in a relative effect because we're comparing the combination vaccine components to the separates.

So our confidence interval for analysis needs to be consistent with the hypothesis. It's a two-sided confidence interval on a ratio, and our hypotheses were about a ratio. Our analysis should tell us something about a ratio.

We're not interested in point estimates, not for inference. We're not interested in geometric means for the individual groups and their confidence intervals. We want our analysis to be consistent with our hypotheses.

That's another reason why it's important to specify your hypotheses because your hypotheses guide what your analysis will be, and just as important, your hypotheses guide you in how to interpret the data.

So we have here a one minus two alpha competence interval that provides a test of size equal to or less than alpha, and the lower limit is the important one for evaluation, and that's just because the combination is in the numerator of the ratio. I could have specified the hypotheses the other way. I could have put the combination in the denominator. Then I would flip those inequalities around and we'd be looking at the other confidence limit for evaluation.

So it's important to know what your hypotheses are because if you don't know what those are, you don't know which limit you need to be looking at for evaluation, and so we look to see: does the lower limit exceed theta naught? If so, then we can conclude the alternative, that combination is not inferior, and then the study has been successful.

So our interpretation is consistent with the hypotheses. Our analysis is consistent with the hypotheses. Note the harmony here. The hypotheses are specified to be consistent with the decision making process we anticipate making. Our analysis is consistent with the hypotheses. The interpretation is guided by the hypotheses. Everything fits together harmoniously, kind of like a well orchestrated

symphony.

That's the beauty of statistics when we do it right.

For a difference in proportions responding, and this may be the most relevant for today's meeting, we may specify the alternative in a manner like this. We're interested in estimating delta, which is the proportion in the combination group minus the proportion in the separate, and we want to see if that proportion, if that difference is greater than some negative quantity delta naught.

And again, the difficult part is not specifying the hypotheses. It's deciding what should that clinically meaningful delta naught be. Should it be .25? I saw that years ago when I first started to work in CBER. Should it be .15? Point, ten we commonly use now. Some people would like for it to be even smaller, .05, but you know, what should be the appropriate one?

Another question is: should delta naught, that clinically meaningful difference, should that be the same for an antibody greater than or equal to .15 micrograms, and also for greater than or equal to one microgram, or should we have a different delta naught for those two?

Also, should delta naught be different for different target populations? Those are difficult questions to answer. See, figuring out that these should be designed and analyzed as non-inferiority trials was the easy part. Some of these other questions are the difficult ones.

Again, we make our analysis consistent with our hypotheses. This confidence interval is not on the individual proportions. Our hypotheses are about a difference in proportions, and so our confidence interval has to reflect that. Our confidence interval here is on the difference between the two groups.

Again, the lower limit is the important one for evaluation simply because we have specified our hypotheses so that the combination -- it's saying the combination one is the separate. If I had reversed those and said the separate minus the combination, then everything would just get flipped around, and we'd be looking at the upper confidence limit.

And so we evaluate by looking at the lower limit and ask: does the lower limit get seed minus delta naught. That's what our alternative hypothesis says we should do to evaluate this confidence

interval. If minus delta naught is minus .10, then looking at that lower limit in red up there, minus .08, then that would lead us to reject our null hypothesis and conclude that the combination is not inferior to the separate.

However, if minus delta naught is set, is prespecified at minus .05, then we would not reject the null hypothesis, and we would conclude that the combination might be inferior.

Now, some issues to think about is what is the choice of alpha. Should it be .05, .025, or something else?

The reason that I put this in here is that in your briefing document you have the confidence intervals from some of the studies provided there, and some have 95 percent confidence intervals, some have 90 percent. Just be aware that a 90 percent confidence interval corresponds to a Type 1 error of .05, while the 95 percent corresponds to an alpha of .025. Your 95 percent confidence intervals will be slightly wider than your 90 percent, and so just keep that in mind when you're looking at those data.

Another issue that is problematic is the issue of multiplicity because these combination vaccines have a lot of antigens in them, and some have

multiple serotypes, and so the CFR requires that we demonstrate non-inferiority with respect to each component. So we are doing multiple comparisons. The hypotheses that I showed you are for one component at a time, but in fact, we're evaluating all of them simultaneously, and that presents a problem.

I'm not going to get into that more today. We will be talking about that some more next week at the combination vaccine workshop.

And then one of the most difficult issues is, as I said, the choice of your clinically meaningful differences, theta naught and delta naught. If we have a reliable immune correlate that we can count on, that would certainly be helpful.

Another issue is what we call immunological creep, and the best way that I can explain what that is is to show you this. Now, this art work is complements of Dr. Goldenthal, but I think it shows pictorially what we're talking about very well.

Suppose we start out with a combination vaccine A that has components A and B in it, and as each new vaccine is evaluated, the new vaccine is allowed to be within ten percentage points inferior to the preceding vaccine and still be acceptable.

Now, suppose each successive vaccine is inferior, but within that ten percent amount. We could eventually end up with a vaccine that is quite a bit more than ten percentage points inferior to the beginning one, and that's an important point to keep in mind when we're deciding how much we want that theta naught and delta naught to be. How much of a drop in immune response are we willing to allow?

I think that's -- yes, that's the end of my talk.

CHAIRMAN GREENBERG: Thank you, Dr. Horne.

After this we have an open public hearing. Before I go to that, are there any questions for Dr. Horne?

(No response.)

CHAIRMAN GREENBERG: I thought so.

(Laughter.)

DR. HORNE: Everybody understood everything.

CHAIRMAN GREENBERG: There's going to be a test before dinner.

(Laughter.)

CHAIRMAN GREENBERG: We have a couple of people who wanted to do some presentations in the open public hearing and a couple more. So the first is, as

I understand it, is Dr. Dan Granoff; is that correct?

Since we have -- Dan, how long will you -- good. Make it seven.

I'd just like the representatives from the CDC have asked me whether it would be helpful with the committee to very briefly review some epidemiology data from the United States to contrast and compare with the data you saw from England and Germany, and I see lots of yeses and no noes. So that will follow.

DR. GRANOFF: Thank you.

I appreciate the opportunity to come here and speak.

For the last year and a half I've been at Oakland Children's Hospital Research Institute as a research scientist. In the spirit of disclosure, I also have consulting arrangements on specific projects with SmithKline Beecham, Aventis Pasteur and Chiron Vaccines.

I really want to comment on two areas. One really relates to the discussion we just heard on statistical considerations.

Is there a way to just shift the slide?

Because there's been a lot of emphasis on carrying the Haemophilus antibody responses of the combination vaccine to the specific component given

separately, with the idea that this is the way to look at whether you're affecting the quality of the component.

But I would raise two issues. One, with Haemophilus conjugate vaccines, we have a very good understanding of the quality and quantity of an antibody and its function, and we have a precedent for licensing new Haemophilus vaccines based on measuring anti-PRP antibody responses, not getting into the question of what the definition of the magnitude of the response should be for this licensure.

But, for example, for vaccine A, we have two vaccines, the HbOC and PRP out of membrane protein that have been demonstrated in clinical trials to be at efficacious. Vaccine B can be then licensed based on comparing the compared immunization, immunogenicity to Vaccine A, and you've heard the difference allowable being ten percent.

Now, the question is in making a combination vaccine with Vaccine B is the appropriate comparison back to the Vaccine B given separately, or is it to one of the vaccines which have been demonstrated to be efficacious, and I think you could make a case to avoid immunologic creep, although I'll show you there are some other sources of immunologic

creep as well.

But you can make a good case that really the appropriate comparison for Vaccine C, the new combination, is not the component given individually, but to go back to the very way that we would take any new Haemophilus conjugate vaccine and approach its licensure, whether it's in combination or individual and show it to be at least equivalent to a conjugate vaccine in which efficacy has been demonstrated in a clinical trial.

Now, having said that, what I'd like to do now in the next five minutes is to really present some data from my own laboratory that there's been excellent control of Haemophilus disease. Well, that's CDC data, but that there's been some trend for declining Haemophilus antibody responses to at least some licensed Haemophilus vaccines in the population.

This is a slide from MMWR in 1998. You've heard it already today, indicating that in the two years there are 144 cases of Haemophilus disease detected in the U.S., representing a 99 percent decline, and of those children with vaccine histories, only 27 have had more than three doses of vaccine.

So we really a very, very effective vaccination strategy in this country with the

currently licensed vaccines.

Now, I don't have market data exactly, which vaccines are being given, but there are a number licensed, but one of the major vaccines that is used that really probably represents the majority of the U.S. market is the Wyeth Lederle Haemophilus influenza Type B oligosaccharide (phonetic) CRIM or HbOC vaccine.

And show here graphically are data from my laboratory on a larger number of studies done from the 1980s on a pre-licensure lot, 1990 shortly after licensure, and more recently of this vaccine being given to infants at two, four, and six months of age, and looking at geometric mean antibody one month post dose three.

All of these are done by a radioimmuno assay, and actually a single technician over at the time has been running these initially in St. Louis and more recently in California. The Xes represent where these are separate administration always of the Hib conjugate given either separately with DT whole cell vaccine or DTaP vaccine.

And what you can see is pre-licensure and we reported this -- there were very high levels of antibody, geometric mean over 20. By the time the

vaccine was licensed the range was more in the five to six range, and there's been a steady decrease over this period to the most recent studies.

Now, these are the same trials shown as the percent of infants achieving more than one microgram per mL one month post dose three. Initial study approached 100 percent. Back right around the time the vaccines were licensing we were right around 90 percent, and there was a decline around to 80 percent and to more recently around 60 percent with fairly narrow confidence intervals.

Now, this slide summarizes the data from the most three recent studies that we've done with the HbOC vaccine assayed at Children's Hospital, Oakland Research Institute showing the study sites and the geometric mean, the number of subjects, infants, in these trials, the geometric mean antibody, and the percent greater than one.

And I'll point out that the most recent study was a U.S. multi-center study. It was done actually as part of an infant formula study involving 254 infants at multiple sites, and the geometric mean was 1.74 and 61 percent were greater than one microgram, and I've contrasted those results to a number of the SmithKline combination vaccine studies,

DTaP-Haemophilus, DTaP-Haemophilus-IPV, and then the combination that contains also Hepatitis B.

And what you can see is that the levels of antibody being achieved in these various studies, including a U.S. study, are really quite indistinguishable from what's occurring in the United States in at least one large trial with the Wyeth HbOC vaccine.

So when you compare, in each one of these studies when you compare it to the separately administered antigen contained in the conjugate, you show a depression of around 50 percent, but at least based on studies done in one laboratory, SmithKline, the levels achieved are really not very different than what we're seeing in U.S. populations getting a licensed Haemophilus conjugate.

Now, one question would be that these are different laboratories and could that be the explanation, and so to look at that, serum samples from one of the SmithKline studies was sent to my laboratory and assayed by the radioimmune assay. Those are on the Y axis, the CHORI values. SmithKline values are here, a line of identity would show an identical result in the two labs, and there's really no significant difference in the two laboratories. If

anything, we are measuring a little bit higher than the SmithKline.

So that the levels I'm showing you are really not being overly -- I'm not understating them. They seem to be quite representative of what SmithKline is finding with their combination vaccine.

Now, these are the same data that I showed you, the top three studies, and is my laboratory the only one to see these low antibody responses?

Well, the answer is no. Show on this, the lower line, the results that were presented to this committee in support of licensure of the acellular pertussis vaccine Certiva in which 249 infants in the U.S. at multiple sites received Certiva as a separate injection with the Wyeth HbOC vaccine, and you can see the geometric mean reported here, but only 61 percent of children were achieving antibody levels over one microgram.

So in summary there really don't exist surveillance of Haemophilus responses to different vaccines once vaccines get licensed at least systematically. And so what I've tried to give you is a glimpse of at least one laboratory's experience looking at a specific vaccine that is licensed that represents a dominant part of the U.S. market.

And what we see is that the antibody levels that are currently present with that vaccine are really very similar in magnitude to that being reported in the different trials with the combination vaccines.

So it seems to me that one logical question to ask in terms of combination vaccines, and I think it needs to be done in a systematic way, not necessarily through historic data, but does that vaccine -- not necessarily whether it's giving depressed responses to the individual antigen given separately, but how does that vaccine relate in terms of its Haemophilus responses to what is being seen in children getting Haemophilus vaccines now, and if the combination vaccine is producing the same magnitude of the response as achieved by licensed vaccines and if the quality of the antibody is measured by ways that we know how to measure it, avidity, bacteriocidal, animal protection is similar to the licensed vaccines.

I think we could approach the licensure of that vaccine in a very similar way that we would approach any new Haemophilus vaccine based on equivalence to a vaccine that's shown to be efficacious in a clinical trial.

Thank you.

CHAIRMAN GREENBERG: Thank you.

Question? Dr. Breiman?

DR. STEPHENS: Dr. Stephens.

CHAIRMAN GREENBERG: Oh, I'm sorry.

(Laughter.)

DR. STEPHENS: He's over there.

CHAIRMAN GREENBERG: He's much more handsome than I am.

DR. STEPHENS: Why do you think this is occurring? I mean why do you think this overall decrease is occurring?

DR. GRANOFF: Well, of course, I don't know, and there are a myriad of possibilities. I mean one of the most obvious is whether there has been some change in the vaccine over time, and that I can't address.

Then the question is is there something different about infants in the U.S. getting vaccines today than getting them before they were licensed, right at the time that they were first licensed, and Katy's question, I think, was really very germane. What is the effect of conjugate vaccine on some of these cross-reacting bacteria that are in the gastrointestinal tract?

I don't think it's a question of Type

colonization because the rate of colonization of Type B in children less than six months at the time they're immunized before we had vaccines was very, very low. So that's not a source of priming. I think John Robbins has really said that.

But these cross-reacting organisms could be an important source of priming, and if conjugate vaccination actually affects GI colonization, then we may be having a different response to the conjugate vaccine.

I'm sure there are other potential explanations. The switch over from whole cell pertussis as a separate injection to acellular pertussis could also have had effect in terms of priming to the carrier protein, but anyway, I don't have an explanation.

CHAIRMAN GREENBERG: Dr. Levine.

DR. LEVINE: Orin Levine.

I guess I'm impressed a little bit today as one of the threads through some of the presentations in the degree to which there's variability in immune responses to Hib. In one of the presentations today we saw that even within one multi-center study there were fivefold differences, and we weren't quite sure exactly what to make of them.

I'm wondering if in your experience with some of the multi-center studies if you have seen differences when analyzed by the study site.

DR. GRANOFF: Well, certainly in one of the studies we reported where there was a comparative immunogenicity trial in Minnesota, Dallas, and St. Louis. We did have a site variation in, I think, the Minnesota children, and I think it was higher, but I'm not 100 percent sure of that for one of the vaccines, but it wasn't really clinically significant.

You know, we were talking about maybe four micrograms compared to six, and there was large sample sizes, and you can show statistical significance.

I just would emphasize that one of the studies I've just presented, you know, had more than 250 infants. It was at multiple sites over the country, and there there were no real variations between the sites, and these children were getting vaccine that you purchased.

So if you asked the question what are the antibody levels being achieved in the population currently with licensed vaccines, I mean, I think this study is reasonable for that particular vaccine, and when taken together with the other studies, the Certiva study, which was a different lot of HbOC, also

done in multiple sites, I think that the conclusion that there are a large number of children getting much lower levels of antibody in the population today than compared to when these vaccines were licensed is inescapable.

And to follow up that point also is that the Eskimo data that we heard -- sorry -- the Alaska data we heard today, you know, really relied on looking back at data from ten years ago, and I think we really do need modern immunogenicity data on what the vaccines are currently doing if we're going to try to sort some of those variables out.

CHAIRMAN GREENBERG: Dixie.

DR. SNIDER: Yes, Dan. Just to follow up on that point, I appreciate what you're saying with regard to the immune responses one gets in U.S. children, Swiss, German, and so forth, and yet as a public health person, I'm concerned about Native Americans in Alaska.

I'm also concerned about people in Africa and others who might be eligible to receive some of these vaccines, and I just worry about being too provincial in our view about what kind of immune responses might need to be achieved in various populations to achieve protection because as has been

mentioned, you know, once a country achieves a certain level of immune responsiveness in the herd and also has a certain socioeconomic standard and so forth, that country might be able to tolerate a vaccine that's not quite as good, if you will, than a country that is not so fortunate from a socioeconomic standpoint or from an immunologic standpoint because of nutrition and other things.

DR. GRANOFF: Well, I would just say though that we have vaccines currently that we're using that are achieving these levels, and so the question is should we exclude new vaccines that are achieving the identical levels.

DR. SNIDER: And my point is exclude from the U.S. or exclude from another country, and I think those are different questions.

DR. GRANOFF: I think they're different questions. I mean at least most of the data I've seen from developing countries is actually the opposite, at least in Turkey, at least in South American. There's actually higher responses to these vaccines than we see in the U.S.

CHAIRMAN GREENBERG: I have a couple of questions, but Ms. Fisher is first, but just vis-a-vis design, is it a fair design to take a combined vaccine

and compare it to what you're seeing as levels in the country or don't you actually have to design that as a trial, and has that been done?

DR. GRANOFF: Yeah.

CHAIRMAN GREENBERG: I mean you're not really comparing the same populations, and so are you sure that --

DR. GRANOFF: No. I think that's a very valid point.

(Laughter.)

DR. GRANOFF: I am presenting this data as a form of hypothesis generation. I think that it would be up to manufacturers to prove using different study designs that they would have to discuss with FDA is there a vaccine achieving comparable levels to vaccines that are currently licensed, and I guess I am really saying that to me that's the more logical target than to say if you have the individual component that we're using.

Suppose you have a very good component that happens to be terrific and you get a 50 percent drop. Does it really matter if that 50 percent drop is higher than the other licensed vaccines? And why should we be approaching combination vaccines in a different way than if I came to the FDA with a new

Haemophilus conjugate where that wouldn't be the criteria? I would be able to compare it to a licensed vaccine.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: Well, one of the things that has changed in the last decade particularly with regard to infants and young children is the addition of Hepatitis B vaccine, the birth dose and at one month and, you know, the first year of life, and has there been any thought to whether or not that has affected the whole profile because Hib is not given -- you know, it's given within this context of Hepatitis B vaccine being given at birth and one month?

DR. GRANOFF: Yes, I believe the data I showed you at least in the large multi-center study, that Hepatitis B was not given concurrently, but I can't really comment on where --

MS. FISHER: Not concurrently, but it is given.

DR. GRANOFF: It is being given to the children the first year.

MS. FISHER: I would change the immune -- the immunological response of the child might be different because of the addition at one month of the Hepatitis B.

DR. GRANOFF: Yeah, I can't comment on that. I don't have any data at all.

CHAIRMAN GREENBERG: Does anybody have data relevant to that in the audience? The hypothesis would be that Hepatitis B vaccination lowers immune response to Haemophilus vaccination. I will bet that there are people in the audience who have that somewhere in there.

Okay. Well,m that's an interesting hypothesis, and somebody should look at it.

I've lost track of who was raising their hand. Dr. Robbins.

DR. ROBBINS: I'd like to just present the data that Dan presented in a different light, and that's this. Even today there is no unambiguous method for assigning a physical constant to the conjugate vaccines that predicts their potency. It's done indirectly and by secondary effects, and I don't think we'll be able to achieve that kind of physical-chemical characterization when the polysaccharide is made from a natural substance. It's too heterogeneous.

And therefore, I predict from our studies now with Shigella that the only way we can achieve that kind of characterization and precision in

predicting is to have a synthetic vaccine.

It's been done for Haemophilus. I don't know why it's never been used, but I'll predict that when it's done properly it will be far superior to the materials made by the current method, and --

CHAIRMAN GREENBERG: Far more predictable.

DR. ROBBINS: No. More immunogenic. I'm sorry. Excuse me. It will be more immunogenic than the current products, and that you can predict or give a physical constant to the preparation which would allow you to evaluate its performance rather than what we're obliged to do now, and that is to do trials of immunogenicity.

It's more expensive, but it will be much better.

CHAIRMAN GREENBERG: Okay. We have one or two more speakers before we get to the questions. So I'm going to, unless there's a burning issue, I'm going to move on to Dr. Bud Anthony.

Dr. Anthony.

DR. ANTHONY: Thank you, Dr. Greenberg.

I have no overheads or slides, and I'll be brief. May I speak from here?

CHAIRMAN GREENBERG: Sure. Could you simply introduce yourself?

DR. ANTHONY: Yes, certainly.

CHAIRMAN GREENBERG: And talk about your affiliations and whether you might have any conflicts.

DR. ANTHONY: Well, I am Bud Anthony, and for the last two years I have been affiliated with the Biologics Consulting Group in Alexandria and have some clients among the manufacturers.

Aventis Pasteur, I believe, is the only client that I've been involved with that has interest in these vaccines.

The consulting bit has gone on for two years, but I spent most of the 1990s at CBER, and I'd like to speak from that experience if I may.

Several significant things happened when I was there. One was in 1993, the year of the first conference on combination vaccines, and the first surfacing that I was aware of of 601.25, the regulation that Dr. Horne cited in her elegant presentation.

Incidentally, my reading of that regulation is that it was written after the thalidomide disaster. It applied to drugs that were on the market that had never been tested for efficacy, and it had no, when written, no relevance to combination vaccines.

It is, however, a perfectly reasonable statement that the components should or, rather, the combination should match the components. I wish I had it to quote it. I cannot quote it, but Dr. Horne did, and that is the essence.

When carried to the extreme, and I think this is what has happened, this assumes that every combination will be made of licensed components, and it puts those combinations at a disadvantage as we've heard relative to noncombination vaccines or to vaccines made -- combinations of entirely new components where the competition is what's on the market.

And in answer to your question, Dr. Greenberg, PRP-T was licensed because its immunogenicity matched that of the conjugates that had been previously licensed and which had been effective in efficacy trials.

One of the other things that occurred shortly after the combination vaccine workshop was that a task force at CBER went to work to develop the guidelines which have been issued as a guidance document and which I do think heavily influence the policy.

The interesting thing about the

guidelines is that they are written as though every new combination will be composed of licensed components, and again go back to this emphasis of comparing immunogenicity and the lack of an efficacy trial of the combination with the components.

There is one statement that a combination can be licensed if its immunogenicity meets what are accepted as protected levels, but that is really kind of buried in a number of pages of how it will be compared with the component.

The upshot of this, I think, is the disadvantage that components of previous licensed products face the obsession with these types of comparison to the exclusion of other comparisons and other studies, such as what are the existing levels, what are some of the public health considerations and what are some of the clinical considerations?

Now, I would not wish on my colleagues, my former colleagues and my friends at CBER, that they rewrite the regs. I think that reg. is perfectly fine, but I do not think it needs to be interpreted as meaning that you must demonstrate equivalence or non-inferiority and always in control trials.

I think the guidelines -- forgive me -- are badly out of date and do not really address the

issue. I think this obsession with the kinds of comparisons that we've heard about don't make much scientific sense or regulatory sense or common sense.

Thank you.

CHAIRMAN GREENBERG: Thank you.

I'm just going to move on because I think -- no, no, we have one more. There is somebody else, at least one other person.

So is the CDC person ready to do a quick tutorial?

DR. BISGARD: We just have a few overheads.

CHAIRMAN GREENBERG: And this is Dr. Bisgard, right?

DR. BISGARD: Yeah. Just to start off with, since 1994 all 50 states have been reporting Haemophilus influenza invasive disease, and over the past few years we've done a better job at serotyping or getting information on all of the reported cases so that the number of unknowns, which is in the pink, the unknown serotypes has gone down. 1999 data is provisional. We expect about 75 percent to 80 percent to be serotyped, and the Bs have gone down, and some of the bumps here are from the Alaska group.

And this just shows that of the Bs there

isn't that much difference between these other racial and ethnic groups and then the Native Americans have a higher incidence.

These are just 1998 data and most of our cases are in these very young infants. In 1998 we had 60 Hib cases, and of those the majority were less than one year of age. So it seems that the booster probably has some effect in preventing disease.

And then finally in these 60 Hib cases, most were too young. We did have about 15 vaccine failures, and we also have some that we don't know the vaccination history, but probably they were not vaccinated or were under vaccinated, and that's all I have to say on the data.

Now, Nancy Rosenstein has a little bit of data from the active surveillance sites. The NCID is trying to collect underlying conditions on all the Hib cases, and here is age in days and over here is the type of disease source of the isolate if it's Type B or unknown.

Number of vaccination doses. So these older kids have gotten three or four doses, and we've tried to assess what underlying condition they had. It seems that there are a number of pre-term infants, and we've looked at a few of these. They are like 30

weeks, 32 weeks. So they aren't really preemies. Preemie-preemies is what I want to say. There's some hardware, HIV, asthma, and I know there was another one as IgA deficiency.

And then 1999 data, we don't have much information on the vaccine failure cases yet. When was the hardware disease Group B strep as well.

Questions?

CHAIRMAN GREENBERG: Okay. Actually do you want to start your questions now?

Fine. Let's do the questions of Dr. Bisgard, and then we will open up to the public and then we'll get down to business.

Dr. Kohl.

DR. KOHL: I don't know if you can answer this, but how accurate is the surveillance? What percentage of cases do you think that you're talking or collecting?

DR. BISGARD: It's not 100 percent. We would say, I would guess, I would say like 60 percent. Now, active surveillance they do a better job, but they still have some unknown serotype. So active surveillance is able to get the laboratory cases. Ninety-eight percent is what they estimate, and then serotyping on 70 percent.

CHAIRMAN GREENBERG: Dr. Breiman.

DR. BREIMAN: Is there an estimated rate in the unimmunized population so that we could compare with what Dr. Heath presented earlier?

DR. BISGARD: The vaccination coverage by two years of age for three or more doses is 95 percent. So we don't have a population per se that we look at that's unimmunized and that these cases came from within a certain group of unimmunized children.

There was a recent outbreak in Pennsylvania, anyway, that NCID has investigated amongst Amish, and most of those were unimmunized, and I think there was what, five case? There's five cases.

DR. ROSENSTEIN: Six cases, five Amish people between --

CHAIRMAN GREENBERG: Identify yourself, please.

DR. ROSENSTEIN: Nancy Rosenstein from NCID.

And there were six cases in December and January of this year in central Pennsylvania, and five of them were among Amish people.

DR. BISGARD: And the coverage rate is like less than 25 percent at two years of age.

CHAIRMAN GREENBERG: Dr. Fleming, and then Dr. -- well, Dr. Ferrieri and then Dr. Fleming, however you want to adjudicate.

DR. FERRIERI: This will be more complicated perhaps. My question for you is if you have data on Native Americans in the Southwest U.S., I'm intrigued by the data from Alaska with background increases in colonization and increased incidence of HIV disease. What do we know that's happening in this other population? Do you have any information?

DR. BISGARD: Some of those Type B cases were from the Native Americans in the Southwest. I have not been involved in the carriage surveys that have been done in those, but maybe Orin Levine would know those data at least.

DR. LEVINE: Yeah, there are investigations going on right now to characterize colonization in the Navajo and Apache in the context of a large pneumococcal trial vaccine that's going on right now. At this point in time I don't know the latest data on that, but I can tell you that the immunization regimens that they've been using there are a little bit different than what has been used in Alaska.

They have been using PRP-OMP for the first

dose and then HbOC in combination with DTP for the subsequent doses for some time, and one of the reasons for that investigation is to see if we can tease out to what extent differences in vaccine regimen may be reflected by differences in carriage.

CHAIRMAN GREENBERG: Okay. We're only going to have a few more questions.

Dr. Fleming.

DR. FLEMING: Could you flash up a slide that went by very quickly that was showing the distribution of the Hib cases by age in I think 1998 or something along those lines? It looked as those we had a substantial fraction that were occurring in ages less than six months.

DR. BISGARD: Right. I think most of our cases do occur right here.

DR. FLEMING: If you go back to the previous one, it's --

DR. BISGARD: It's almost half.

DR. FLEMING: It looks like, just eyeballing it, about half.

DR. BISGARD: Right.

DR. FLEMING: Okay. Thanks.

CHAIRMAN GREENBERG: Okay. Last question, Dr. Edwards.

DR. EDWARDS: Could you just tell us a little bit about the 15 vaccine failures, what vaccines they may have gotten? I think that was the slide or the overhead you were putting up, but you didn't comment on.

DR. ROSENSTEIN: So I could do, but I didn't, a line listing of all of those 15 cases and tell you what vaccine they got at which point in time. I guess the point is this is a population of 26 million. So it's a large population, but we don't have specific information on vaccine use in that population, and so I'm not sure how to interpret this data.

CHAIRMAN GREENBERG: Okay. I'd like to ask if there's anybody remaining in the audience who wishes to talk to us. Could you go to the microphone and identify yourself?

DR. SIEGRIST: Dr. Siegrist from the University of Geneva, Switzerland.

We have seen evidence today that infants given combined vaccine --

CHAIRMAN GREENBERG: Excuse me for interrupting, but I've made a decision that I will ask all speakers from the audience whether they have any conflict of interest.

DR. SIEGRIST: I have been and I am a scientific advisor to a number of vaccine companies, SmithKline Beecham, Aventis Pasteur, Wyeth Lederle, and if not, I work in a university environment.

CHAIRMAN GREENBERG: And you're here as a university person or as a consultant to one of those companies?

DR. SIEGRIST: As university person. I worked with Dr. Eskola in the paper that was presented earlier today.

And I wanted to make a question, in fact, really. We have seen evidence that infants given combined vaccine respond to the vaccine in the same proportion as other children, that they are primed normally, and that they produce antibody of normal functional capacity.

And the question that really remains and that no one can address, I guess, which is a concern, is whether the lower antibody responses that are induced by these combined vaccines would be sufficient to control carriage, and I don't think anyone has the data.

However, I am surprised that little attention has been given to the fact that these children will be boosted in the second year of life

and that they respond by the booster with high antibody responses which are similar to the one raised in control children.

So my question would be: is there any reason to suggest or to fear that inducing high antibody responses in the second year of life would not be sufficient to control carriage and thus, to protect the few children who were either nonresponder or non-vaccinated?

CHAIRMAN GREENBERG: Good questions. Is there anybody who has a good answer to that?

Dr. Robbins, the source of all answers.

(Laughter.)

DR. ROBBINS: I just want to tell you a little about the dreams of my colleague and myself. Haemophilus influenza Type B as we know does not exist in any other species except humans. There is no zoonosis. There is no reservoir of the organism, and as you can see, as we start to achieve widespread vaccination, we are eliminating the disease and the organism gradually.

So it's not inconceivable to think that this organism could be eradicated from the earth.

I think that in looking at vaccination policies we should try to eliminate as many cases as

we can in every country. It's easy to loosen up, but I think at this stage with this potential to eliminate this pathogen we should try to have the very best, the maximum vaccination policy possible.

CHAIRMAN GREENBERG: Okay. Thank you, Dr. Robbins.

And are there any other people who wish to address the committee? Yes.

DR. MEYERHOFF: Yes. My name is Alan Meyerhoff. I'm with an independent research company here in Virginia called Capital Outcomes Research.

With respect to your question of conflict of interest, we perform work for a variety of different pharmaceutical manufacturers, and that has included SmithKline Beecham.

I just have a comment to make. I was unfortunately not in attendance this morning when I understand there was a question about the benefits of combination vaccines. I just wanted to state that we are just now completing a study that is assessing one combination vaccine for both it's epidemiologic and economic effects, and we found that there are certainly increases in coverage rates and some significant economic advantages in terms of reduced costs primarily and reduced vaccine administration

fees and in reduced visit fees, those primarily being -- the visit fees being indirect costs associated with lost productivity of the parent taking the child to the visit.

And lastly I note that although it's hard for us and others to quantify, there is also a benefit in respect to reduced pain and emotional distress associated with the number of injections.

CHAIRMAN GREENBERG: Thank you.

I am very pleased to hear that, and my own feeling is that data such as yours and others are very much needed, real scientific data weighing what the benefits are because this discussion primarily, with the exception of what you just said, which of course is not yet data -- it will be data -- has been one sided. You make it change because of a reason, and these are the reasons, and I don't have as much data as I should have, nor does the committee as to what those are.

I would also say that we are getting more and more sophisticated at measuring things like pain, stress, et cetera, and that those should not be avoided as measurable entities that can be quantitated in some way so that you get a feeling when you're looking at vaccination, multiple vaccinations.

So I applaud your company, and I would ask other academics, et cetera, as this gets to be a bigger and bigger problem that we really need that other side to weigh. It's very hard to have this discussion in the abstract.

Dr. Snider.

DR. SNIDER: Just with regard to data, there are some data and that is if you just look at the vaccination schedule for the year 2000 which was just published and compare that to one for five years ago you'll see that a number of vaccines have been added, and indeed there are a number of vaccines as you are well aware that are in the pipeline that are some even nearing the point where they will be used.

So that with regard to data we do know that the number of vaccines that are currently recommended and presumably soon will be recommended continues to increase, and in that regard, I'm sorry we don't have it with us, but around the issue of number of immunizations, when we were considering the switch from OPV to IPV, some studies were done with regard to physician and provider and parent acceptance of increased numbers of doses, and there are quantitative data on that which could be provided to the committee.

CHAIRMAN GREENBERG: I was told that, in fact, the data -- this is not my field -- but that the data shows that that switch did not lead to a negative effect. So an immunization, a systemic parenteral immunization was added without subsequent decreased rates. So is that correct?

DR. SNIDER: That's correct, and in terms of coverage rates, there was no change. My point was that you were looking for data, and those are some data.

There also were data though with regard to -- that are interesting that have to do with providers being very reluctant, much more reluctant than parents to add additional injections. So my only point is there's a body of data relative to your point. So we could make it available.

CHAIRMAN GREENBERG: So maybe at some point at a next meeting or in the meetings in the future where we have a little more time, somebody at the FDA could fill us in on that because I think this is going to come up over and over again before us, and that would help educate us.

Any other people in the audience?

I guess I have no ability to interfere with people in the audience so we will be here until

everybody can speak their peace, and I want you all to present, but I would like to make it as please be sure you feel it's an important message.

DR. BOGAERTS: Thank you for the opportunity.

Hugues Bogaerts from SmithKline Beecham Biologicals, the conflict of interest being cleared.

We have seen data today, and there are more available that many of the cases that still come down with invasive Haemophilus disease in vaccinated children are actually children that have been incompletely vaccinated.

Further, on the comment that was given on compliance, I think we can do a better job by insuring that more doses are given to children who started the vaccination process by, indeed, switching to more elaborate combinations, including those who have Hib.

If I may try again, remembering the experience of this morning, to show you three slides there, we see here a study that was conducted not too far away from Germany, namely, in Austria, and two doses of the combination which is Infanrix-Hib has been given here at three and five months of age. these are children who deliberately for the sake of the study only got two doses of Hib and, of course,

they got a third dose of DTPA along to complete the recommended vaccination schedule in that country.

The next slide will show us what the antibody titres in those children were prior to the vaccination. Then at the completion of the two doses, and we are here at 1.3 micrograms per mL going down as expected and then going up again when the booster which is routine in that country is given between 15 and 16 months of age.

The point that I want to make is that the 1.3 geometric mean concentration, and that is not on the slide, but I do have the data here, corresponds to 93 percent of subjects with an antibody concentration greater than 0.15.

Now, we have seen if we make the bridge between Austria and Germany that the data after two doses obtained in the effectiveness study presented by Dr. Schmitt was in the order of 93 percent effectiveness. So 93 percent of children with a titre greater than 0.15 could eventually lead to 93 percent of effectiveness, which is already a very nice figure.

If I bridge this now to the potential for a combination to insure that children also more often get a third dose, then I think we are in very high spheres of effectiveness that will definitely offset

the potential or the hypothetical lower efficacy that may result from combining the vaccines.

Thank you.

CHAIRMAN GREENBERG: Thank you.

Is there anyone else in the audience that wishes to speak? Yes. Is there somebody else that -- Dr. Ferrieri, I'm sorry. I didn't scan far enough.

DR. BALL: Hi. Leslie Ball, CBER, FDA.

I just wanted to address your last point regarding multiple injections and parental compliance, and there was a paper in December of last month, Archives of Pediatrics Analysis in Medicine, from Philadelphia where they queried 1,000 parents and found out that the children were to receive between two and five immunizations, and what they found was that parental compliance was quite good. About 98 percent of the parents agreed to the number of injections without complaint.

So I think that there are some data that suggest that parental compliance is quite good, and again, this paper echoes what Dr. Snider said regarding physician acceptance, and that may be more of a barrier.

CHAIRMAN GREENBERG: Again, I'll get to it. I think the more data we have the better vis-a-

vis the last speaker who made the point, I think, that combined vaccines would lead to increased utilization or complete immunization.

That is, the data that would support that hypothesis would be terrific to have because that would be very -- that's exactly what I'm looking for, real hard data rather than a theory. It sounds correct to me, by the way, but I don't know that you've proven it to me.

Dr. Insel.

DR. INSEL: The last speaker just showed -- Insel, Rochester -- showed the polysaccharide boost at 15 months of age. I'd be curious if anybody has data showing a polysaccharide boost under ten months of age either with any kind of combination vaccine. I believe Ron Dagan has some data, I think, at ten months of age, but I think there's very little data with boosters under a year of age, under 12 months other than his, but I'd love to hear if there is data under ten months of age with booster -- polysaccharide boost.

CHAIRMAN GREENBERG: Are there any more public comments from the audience?

DR. GOLDBLATT: David Goldblatt from the Institute of Child Health at the University of London.

In terms of conflict of interest, i have received funding, vaccines, and consultancy fees from all the major manufacturers, Wyeth Lederle, NAVA, SmithKline Beecham, and I've --

CHAIRMAN GREENBERG: It's okay. We've got the picture.

DR. GOLDBLATT: Okay.

(Laughter.)

DR. GOLDBLATT: But I'm speaking with a different hat on, which is that I also sit on our government's vaccine advisory committee, and we, of course, have been discussing the whole question of combinations.

Now, rightly or wrongly there is a perception in our country that more than two injections at a single visit is unacceptable, not necessary to the parents who will have them if they see them to be beneficial, but to the health providers and those are actually having to give the vaccinations.

And as you may be aware, we introduced the meningococcal conjugate vaccine into our infant immunization vaccine and a catch up, complained to everybody under 18 months, and that started about three months ago. So all children now require two

vaccinations, two injections at each visit.

We are currently discussing introducing pneumococcal conjugate vaccines when they are licensed, and that, of course, would be a third vaccine because the perception in the country is that that would be unacceptable to health providers and health givers. We, therefore, feel that the whole question of combinations is not an "if" question, but a "when" question, and that's the way we're approaching it in the U.K.

CHAIRMAN GREENBERG: Can I just ask you? I'm probably going to sound incredibly naive. What is the basis of unacceptable? Unacceptable is a very strong term, and what is the scientific basis that led to the entire nation deciding it was unacceptable?

DR. GOLDBLATT: This is through a series of surveys by our Health Education Authority of those individuals who are actually providing vaccines at the cold face, which essentially are immunization coordinators and nurses who are responsible for giving vaccinations, and that's where that information comes from.

CHAIRMAN GREENBERG: And they are public employees?

DR. GOLDBLATT: They are public employees.

CHAIRMAN GREENBERG: Okay. Are there any other questions, statements?

DR. MEYERHOFF: Can I make one other brief comment on this point?

CHAIRMAN GREENBERG: Identify yourself again for the record, please.

DR. MEYERHOFF: Alan Meyerhoff, Capital Outcomes Research.

I'm quite familiar with this literature on the effects of the number of simultaneous vaccines to be administered, vaccine doses. Much of it, in fact, nearly all of it is survey research, and it's asked of physicians in a hypothetical context, for example, just around the time that Hepatitis B vaccine was recommended, and you typically see that many of them will say that they will defer, instead of giving three simultaneous injections at a single visit, they will defer some of those doses to a subsequent visit.

The rub comes in on whether or not those visits indeed occur, and certainly not 100 percent occur, and so there are some coverage rates effects.

That said, the more that vaccines have been added to the recommended schedule, the more injections required, and yet we continue to see an autonomic increase in coverage rates. So I don't

think that we've gotten to that threshold in actual clinical practice. However, at some point we will. We don't know empirically when that is.

And on that note, I think that the changes with the move to four IPV dose regimen and the additional pneumococcal, I think in this current year we're challenging it more than we have before.

CHAIRMAN GREENBERG: Thank you.

Any other issues? Hold on. There is.

DR. LEVINE: Yeah, Orin Levine.

I would just add to that discussion by pointing out that I think not all shots are equal and that parents when they value a vaccine because they really feel like it benefits their child and it's safe are more likely to accept it.

I would point out that in the recent efficacy trial in Northern California in which they asked parents to enroll into a study in which their children would get a fourth or fifth shot at the same visit and only had about a 50 percent chance of getting the pneumococcal conjugate vaccine, they only had about ten percent refusal, and I think that's a good indication of the fact that when parents value that additional vaccine, that compliance and uptake is fairly good.

CHAIRMAN GREENBERG: We are going to have a lot of time for the panelists to talk since we're going to discuss it. So this is the public session. I think we can wait for panelists to express opinions on all of the questions or whatever.

Are there any other public members of the public, not that we're not members of the public --

(Laughter.)

CHAIRMAN GREENBERG: -- who wish to inform the committee of anything?

I have one quick announcement, and then we're going to go to the questions. The announcement is did Jim Williams and/or Ken Guido get their message at the desk? And if you didn't, get it.

Okay. Bill?

So I think now that all of you are completely up to date and know the answers here. Bill Eagan is going to run through the questions, and then what I think we'll do, this is not a yes or no or vote situation. This is just, I think, for the FDA to hear the opinions where any of you have opinions.

So, Bill, why don't you -- shall we just do this one question at a time do you think? And then I think if we go through it all and then go back it will take forever. So why don't we just do one at a

time and see how we do?

DR. EGAN: Okay. Thank you.

Well, these are issues that we've been dealing with in one way or another all day long both in the questions and in the comments and in the presentations, and I guess we're just going to come back to them a little bit more formally.

It's also a little bit difficult because many of these issues are intertwined, and the questions are intertwined, and it may be a little difficult to answer one without going part of the other, but I think it's just unavoidable.

CHAIRMAN GREENBERG: Do I -- I'm happy to do it. I think in the end though. You can't answer them all at once. So why don't we start this way?

DR. EGAN: Yeah, unfortunately we can't give any, you know, yes or no answer.

CHAIRMAN GREENBERG: You need to begin to talk.

DR. EGAN: Yeah, but we'd like to start off with addressing the issue in our assessment of the efficacy of the Haemophilus Type B conjugate vaccines, to ask you to please discuss whether the serum antibody concentrations, i.e., anti-PRP levels or anti-Haemophilus B capsule polysaccharide levels

greater than 0.15 micrograms per mL and 1.0 micrograms per mL, along with some associated percent that your seroconverters to these levels are still appropriate for assessing the efficacy of the Hib conjugate vaccines.

CHAIRMAN GREENBERG: That's a great question, and I think my modus operandi -- and Dixie is sitting there. He is sick, by the way, but he has always been fabulous at framing these things. Are you too sick to step up to the plate for this one?

DR. FERRIERI: May I ask a question?

CHAIRMAN GREENBERG: Sure.

DR. FERRIERI: You said Haemophilus conjugate vaccines, but could you also include in the question combinations including Hib vaccine? Is that your intent, Bill?

DR. EGAN: Yes, it is.

DR. FERRIERI: I think this is important in responding to it.

DR. EGAN: Well, with regard to Question 1(a), I think one answer is to say that we have evidence that with the conjugate vaccines that these particular levels are probably not the best levels for indicating efficacy of conjugate vaccines in the U.S. population, but then the question is, you know, what

alternative numbers are there, and the fact is we don't have any alternative numbers.

So you still come back to these numbers as being useful guides at least as it relates to earlier polysaccharide vaccines, the natural infections, passive immunity where they came from, and for lack of any other correlates. We still have to look at these data and try to interpret in the larger context of all the other data what that might mean.

Clearly there's some point, I would think. There's some threshold below which we would begin to lose efficacy with the Hib conjugate vaccines, but we don't know where that is, and it's very problematic because as we move along with more and more combination vaccines, more and more valencies and potential for interference or reduction in immune responsiveness or immunogenicity of components, we could come across some real problems with recurrence of disease, and we certainly want to avoid that.

That's why approaches like North American Vaccine is proposing seem very, very promising and something I certainly would encourage to continue.

I think that's all I have to say about this right now.

CHAIRMAN GREENBERG: Diane.

DR. GRIFFIN: Well, I would I don't think that there's -- we don't have another criterion to use. These are proven to work. I guess one of my questions would be whether this was in opposition or in addition to looking at geometric mean titres or you only look -- your only criteria is a percent that achieve these levels.

CHAIRMAN GREENBERG: Bill.

DR. EGAN: No, I guess that's another part of it and another complication. I'll ask my colleagues to correct me if I'm wrong, but I think the major emphasis has been on seroconversion to these --

DR. GRIFFIN: To these levels.

DR. EGAN: -- to these fiducial markers.

And as maybe a little bit of a clarification, and again I'll ask for some correction from, you know, Carl or Lydia or someone, that the .15 was looked on as this conservative concentration for protection. In other words, what you'd like the child to have at two years of age, three years of age throughout the danger period, and almost the one microgram as the predictor that you'll maintain that high level throughout this period of risk for disease until the child is three or four.

DR. GRIFFIN: All right. So basically I

would agree, but yes.

DR. EGAN: So without saying the one microgram is the correlate of protection.

DR. GRIFFIN: Okay.

DR. EGAN: Because Dr. Robbins and others have, you know, certainly shown -

DR. GRIFFIN: That that's a correlate of maintaining a protective level. Makes sense.

DR. EGAN: Just to clarify the point.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: From the perspective of individual efficacy, I would agree that these seem, given all the comments that have been made, reasonable, but I think that the issue of effectiveness versus efficacy is an area that we've discussed some today. It remains an important question.

Specifically though in terms of this question, I would think that given the absence of anything else in terms of understanding better conjugate response and the issues that were raised regarding conjugate response, I think these remain useful guidelines.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I don't have much to add. I

was struck by the hypothesis that the conjugate vaccines produce perhaps lower levels of more functional antibody, and yet I was not convinced that we really saw data to support that, and I think that that's something in my mind that should be followed up.

And if there is data or a way to get information about that, I think that would be important in addressing this in the future.

CHAIRMAN GREENBERG: Thank you, Mary.

Dr. Kohl.

DR. KOHL: It's hard for me to go against something that seems to be working so well. I mean we have a spectacular success in this country. Barring strong evidence that there's something that should replace this, I think it's the best we've got.

I would like to see more intensive evaluation of those cases that are breakthrough cases or failure cases very close to admission to see what their antibody levels are like at that point and whether there are other associated immunological defects that explain what's going on because I think those, as Bob Good would call experiments of nature, may have something to teach us that we haven't mined at this point.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: I don't have anything new to add, but I just concur with comments being made that this is probably the best, you know, correlate that we have in our hand at the present time to predict the effectiveness and/or efficacy against invasive disease or Haemophilus influenza Type B. I guess I also concur with the notion that I think it is important to know the GMTs because if the antibody level is meager, which may be able to satisfy these numbers, but that certainly, you know, you'll be concerned about the maintenance of protective levels of antibodies, and then along with what Steve said, that it is important to do a surveillance and find out the reasons for having invasive disease in vaccinees whether they are fully immunized or partially immunized. I think that would provide us very useful information.

CHAIRMAN GREENBERG: Thank you.

Dr. Faggett.

DR. FAGGETT: Yeah, I kind of go along with Dr. Kim, too. I would feel better if we had more evidence in terms of impact on carriage rates. I think that's some data that's lacking, and I think we could be more comfortable in saying that this is a consistent measure of efficacy if we did have that

data.

I would hope that in our acceptance of this that that would be available later. I do go along with it as a measure.

CHAIRMAN GREENBERG: Ms. Fisher, and I cut off Ms. Fisher. So, one, respond to the question, but, two, if the other issues that you were going to bring up --

MS. FISHER: We have a lot more questions.

CHAIRMAN GREENBERG: Yes, we have a lot more.

By the way, just because we have a very big array of experts here, anybody should feel free to say other people have stated their thoughts, and it's not incumbent on everybody to say something if they don't have something good to say.

MS. FISHER: Well, thank you for that introduction.

(Laughter.)

CHAIRMAN GREENBERG: That was not -- that wasn't -- that was not directed at you. It was directed at the people down the line here.

(Laughter.)

MS. FISHER: I'm going to say it anyway

I mean, I think there are unanswered

questions about the biological mechanism of action induced immunity, the Hib, especially in combination with DTaP, IPV, Hepatitis B.

I think today it seems that there's a question about the relationship between serum antibody levels versus memory B cells. I think there needs to be more work on that.

I think we ought to take seriously what's happening in Alaska because this vaccine was developed specifically for high risk populations like Native Americans and the Alaskan Indians, and it seems -- Eskimos, and it seems to me that it could possibly be a warning to us that we have to take seriously why is this happening in Alaska, and does it mean that it could happen to the rest of the population in mainland U.S.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: Well, I think that I feel the most comfortable with the .15 indicating it having a biologic relevance because I think certainly the data that John showed and that others spoke about says that about that level or maybe even lower is what you need to have for protection.

I think these data were derived from studies in unconjugated vaccines and unconjugated

vaccines did not induce memory. So I'm less concerned about the one being a long term measure of protection because I think memory does exist.

But as Dr. Robbins also said, I'm not sure that in every individual child that there's going to be enough time for memory to rev up so that every organism that you see you'll be able to make memory.

So I think they are reasonable numbers, but I think I would favor the .15 and say that that's the most important of the two.

CHAIRMAN GREENBERG: Thanks.

Is that it?

DR. EGAN: May I just ask a clarification?

Would you be happy with a conjugate vaccine after the primary series where you had 100 percent seroconverters to .15 and virtually none to one?

DR. EDWARDS: No, I wouldn't be terribly happy, but I think if you're asking, you know, what the biologic relevance is, I think that that probably has more relevance than the one.

DR. EGAN: Thank you.

CHAIRMAN GREENBERG: Dr. Breiman.

DR. BREIMAN: I'm impressed by the discussion about how much -- how little we know about

some of these key issues, and one of the things that may be of use to CBER would be for this group, maybe a subgroup, a work group, to help to devise a set of research questions, focus questions that could perhaps not immediately, but at least down the road help to answer some of these issues which I think are beginning to get answered, but sort of in a non-systematic way.

I think that whereas I'm sure that physicians would prefer giving fewer vaccines, that if you ask them the question would they want to give a vaccine that's inferior either in terms of effectiveness or safety, by the way, which is something we haven't really talked about, that that would change very much the nature of the response.

CHAIRMAN GREENBERG: All right. Thank you.

Dr. Eickhoff.

DR. EICKHOFF: Well, I feel obligated to say something because I haven't had anything to say so far today.

And I can only echo my colleagues, and in a certain sense this question is probably -- it may be the first and probably the only no brainer of the day. These figures of .1 or 1.0 and .15 are sort of pretty

deeply rooted for the last 30 years. It's important to remember that they were derived from studies with the pure polysaccharide, and some have suggested that it may be different for the conjugate vaccines, and indeed it may be, but I think I at least have seen no evidence today and in the material we were provided that that is so.

I think Steve Kohl's suggestion that it would be nice to have, you know, admission sera from the vaccine failures that are, indeed, occurring, and I completely concur it would be wonderful to have that. The only question is how do we go about getting it or how does anybody go about getting it. That's a tough challenge.

CHAIRMAN GREENBERG: Thank you.

Dr. Ferrieri.

DR. FERRIERI: Well, there's a certain deja vu quality to everything that has happened today. The same people more or less are in the room, and the same issue that we discussed in great depth whenever it was, the early 1990s here, the scenarios where we had all of the breakthrough cases for Minnesota with the unconjugated vaccine, and my memory is, Tom, you got involved in that in a deep way and other statisticians.

But apropos of the issue and the question, I would only add that I can't quarrel with these values based on what we've heard today, but I would urge that more studies are done of antibody induced by the combination vaccine, which we will discuss in more depth later.

And I'm also very interested in the failures of patients who break through and think we should study them immunologically to better understand the nature of their antibody levels and the function of the antibody.

And then in addition, I would echo something that Ms. Fisher said about the transmission and carriage rates that we're seeing. This background noise we're seeing from Alaska I find very alarming also and think that we should put some money into this and try to understand mucosal immunity certainly short of doing nasal biopsies, but that we need to understand in populations with increased carriage rates who have been vaccinated; I think we need to understand whether there is something that has changed, and this should include not just serum antibody, but looking at mucosal immunity.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: I think there's been

considerable evidence here to establish measures such as the .15 as a correlate. I think we want to know though whether it's a surrogate, and I'd like to take a couple of extra moments to answer this question, and at least for me it will assist in answering all the other questions more briefly.

What do I mean by that? Well, what is the question? And I'll take guidance from the Code of Federal Regulations that's already been put forward saying we're looking at safe and effective active components may be combined if combining them does not decrease, dot, dot, dot, dot, an effectiveness.

And from what we've seen, my best sense of effectiveness is -- and I'm going to round these numbers off to make it simple -- we've reduced with the current individual component vaccines the Hib disease occurrence annually from 10,000 a year to 100 a year, 99 percent reduction.

It would seem to me the question in hand is can we alter our approach here in a way that doesn't substantially alter the effectiveness, the 100 going to something greater than that.

So what we're looking for really here is not just that it's correlated. It is correlated. We want it to be a surrogate, meaning that we can