U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

VACCINES ADVISORY COMMITTEE

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MEETING

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Thursday, January 27, 2000

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The meeting was held in the Versailles Rooms I and II, Holiday Inn, 8100 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Dr. Harry B. Greenberg, Chairman, presiding.

PRESENT:

HARRY B. GREENBERG, M.D.

KATHRYN M. EDWARDS, M.D.

MARY K. ESTES, Ph.D.

STEVE KOHL, M.D.

KWANG SIK KIM, M.D.

DIXIE E. SNIDER, JR., M.D., M.P.H.

WALTER L. FAGGETT, M.D.

DIANE F. GRIFFIN, M.D., Ph.D.

DAVID S. STEPHENS, M.D.

PRESENT (Continued):

BARBARA LOE FISHER

INVITED PARTICIPANTS PRESENT:

KRISTINE BISGARD, D.V.M., M.P.H.

ROBERT BREIMAN, M.D.

JAY BUTLER, M.D.

THEODORE EICKHOFF, M.D.

L. PATRICIA FERRIERI, M.D.

THOMAS FLEMING, Ph.D.

PAUL HEATH, M.D.

RICHARD INSEL, M.D.

ORIN LEVINE, Ph.D.

JODIE McVERNON, M.D.

MARGARET RENNELS, M.D.

JOHN ROBBINS, M.D.

NANCY ROSENSTEIN, M.D.

HEINZ SCHMITT, M.D.

MARK STEINHOFF, M.D.

CAROL ZENKO, Ph.D.

CBER PARTICIPANTS PRESENT:

DR. LESLIE BALL

DR. CARL FRASCH

DR. LYDIA FALK

DR. KATHRYN STEIN

C-O-N-T-E-N-T-S

C-O-N-T-E-N-T-S (Continued)

P-R-O-C-E-E-D-I-N-G-S

(8:08 a.m.)

CHAIRMAN GREENBERG: Okay. Good morning, everybody. Good morning. I'd like to welcome you to our first session of the new millennium, and it's an auspicious start. We missed a big storm. This was the easiest commute to Washington I've had in a long time. So maybe the new millennium will be better.

We have a busy day. I'd like to remind all the speakers of my terrible reputation of being very obnoxious when you go over. So please keep to your timetable. Make your presentations crisp and on target.

I'd like to start just simply by having the panel introduce itself, and we'll start down there.

This is a new layout for all of us, and I can barely -- if we get a fog, I won't be able to see who's down there. Is that you, Dixie?

DR. SNIDER: That's me.

CHAIRMAN GREENBERG: Could you start?

DR. SNIDER: Dixie Snider, Associate Director for Science, Centers for Disease Control and Prevention.

DR. GRIFFIN: Diane Griffin, Johns Hopkins

University School of Public Health.

DR. STEPHENS: David Stephens, Emory University School of Medicine.

DR. ESTES: Mary Estes, Baylor College of Medicine, Houston.

DR. KOHL: Steve Kohl, Oregon Health Science University.

DR. KIM: Kwang Sik Kim, Children's Hospital, Los Angeles.

DR. FAGGETT: Walt Faggett, Medical Director, American Preferred Provider.

MS. FISHER: Barbara Loe Fisher, National Vaccine Information Center.

DR. EDWARDS: Kathy Edward, Vanderbilt University, Nashville, Tennessee, home of the Tennessee Titans.

(Laughter.)

CHAIRMAN GREENBERG: Harry Greenberg, Stanford University and the Palo Alto VA Hospital.

DR. BREIMAN: Rob Breiman, National Vaccine Program Office.

DR. EICKHOFF: Ted Eickhoff, University of Colorado School of Medicine.

DR. FERRIERI: Patricia Ferrieri, University of Minnesota Medical School, Minneapolis.

DR. FLEMING: Thomas Fleming, School of Public Health, University of Washington.

DR. INSEL: Dick Insel, University of Rochester School of Medicine

CHAIRMAN GREENBERG: Can we go to our visitors over here?

DR. ZENKO: Dr. Carol Zenko, University of Chicago.

DR. SCHMITT: Heinz Schmitt, University of Kiel in Germany.

DR. HEATH: Paul Heath, St. George's Hospital Medical School in London.

DR. McVERNON: Jodie McVernon from Oxford Vaccine Group.

DR. LEVINE: Orin Levine, NIAID.

DR. ROSENSTEIN: Nancy Rosenstein, Center for Infectious Diseases, CDC.

CHAIRMAN GREENBERG: Oh, my goodness, and can I have the FDA contingent over there on my right?

DR. STEIN: Katherine Stein, CBER.

DR. FRASCH: Dr. Carl Frasch, CBER.

DR. BALL: Leslie Ball, CBER.

DR. FALK: Lydia Falk, CBER.

DR. GOLDENTHAL: Karen Goldenthal, CBER.

CHAIRMAN GREENBERG: Okay. Thank you.

And now we have some administrative notes.

MS. CHERRY: Well, I'd like to thank all of you that braved the uncertainty, in the first place, and then the icy sidewalks and everything else that Washington has to offer in all of its glory right now for coming here to assist us with this meeting.

A couple of announcements: first of all, for any of you who may have cars parked across the street, remember that the Bethesda police are very diligent about checking that lot. So if you ran short of quarters, please get some quarters and make sure you get out there and avoid a ticket.

Another thing I want to ask all of you is please talk into the microphone. The meeting is being recorded, and therefore, it's very important that everything you say, particularly with this large, large panel goes right into the microphone.

I'm about to read the conflict of interest statement. It is not that long this time, but I would ask if you get tired of listening to me, one thing you can occupy yourself with is turning off your cell phones and putting your pagers into silent mode because we really hope that we won't hear those things going off during the meeting.

And finally, for any of you who wish to

make a talk in open public hearing, I want to apologize if the times that we have listed on today's agenda are not exactly what you saw listed in the Federal Register.

We have to make the best guess at the time the Federal Register notice is put together, which is roughly two months before the meeting, and at that time we don't have an agenda. So I've tried to accommodate you.

If you get here for the time that was listed in the Register and you find that it's not on the agenda now, please come see me. We'll see that you get fit in.

And now let me read the meeting statement. Three of our members, Dr. Ada Adimora, Dr. Diane Griffin -- no, I'm sorry -- Dr. Diane Finkelstein, and Dr. Alice Huang are unable to attend this meeting. No temporary voting members have been appointed for today's topic.

The following announcement addresses conflict of interest issues associated with the session on the Vaccines and Related Biological Products Advisory Committee on January 27th, 2000, for the review of the current understanding of the immune parlance of protection against invasive Haemophilus

influenza Type B disease and the clinical significance of reduced antibody response to Haemophilus influenza Type B polysaccharide when combined with DTaP.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the meeting participants. In accordance with 18 USC 208, Drs. Kathryn Edwards, Theodore Eickhoff, and Steve Kohl have been granted waivers which permit them to participate in the committee discussions.

Dr. Margaret Rennels has been granted a restricted waiver which permits her to make a presentation and to answer questions regarding her presentation. She will not be permitted to participate in the discussions.

Dr. Robert Daum has recused himself from this discussion.

Dr. Greenberg disclosed a potential conflict of interest which was deemed by FDA as requiring a waiver, but does suggest an appearance of a conflict of interest. A written appearance determination under 2635.502 of the Standards of Ethical Conduct has been granted to permit him to participate in and lead the committee discussions.

With regard to FDA's invited guests

guest speakers, and those are the individuals along the table over on that side, the agency has determined that the services of these individuals are essential despite their varying levels of conflict of interest. The following interests are being made public to allow those attending this meeting to evaluate objectively any presentation and/or comments made by the guests and guest speakers.

Dr. Paul Heath has received a speaking fee from SmithKline for participation in a Hib vaccine workshop.

Dr. Orin Levine is employed by NIH. He is consultant with Wyeth Lederle on an unrelated topic.

Dr. Heinz Schmitt has grants from SmithKline, Wyeth, Pasteur Merieux, and Merck. He has received consulting fees from SmithKline and Wyeth, speaking fees from SmithKline, and Pasteur Merieux, and Merck, and he is a scientific advisor for SmithKline and Wyeth.

Dr. Mark Steinhoff has grants from NIAID and Merck and contracts with NIAID, Pasteur Merieux Connaught, SmithKline, and Wyeth.

Dr. Carol Zenko is employed by the Section of Pediatric Infectious Diseases at the University of Chicago. Dr. Robert Daum is a Section Chief there.

In the event that the discussions involve specific products or firms not on the agenda and for which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussion. Their recusals will be noted for the public record.

With respect to all other meeting participants, including those who speak during the open public hearings, we ask in the interest of fairness that you state your name and affiliation and address any current or previous financial involvement with any firm whose products you may wish to comment on, and we may follow up on this.

Copies of all waivers and appearance determinations addressed in this announcement are available by written request under the Freedom of Information Act.

And that's it.

CHAIRMAN GREENBERG: Thank you, Nancy.

I want you all to see how quickly and crisply Nancy did her business and to follow suit.

I think we're ready to start. Dr. Bill Egan from FDA is going to set the stage.

DR. EGAN: Good morning. On behalf of the Office of Vaccines Research and Review, I would like

to welcome and thank the speakers, the panelists, and those in the audience who have come here today to address this complex issue of Type B Haemophilus influenza conjugate vaccine immune responses.

Nearly 70 years ago, in 1933, Fothergill and Wright published on the age dependent incidence of invasive Haemophilus influenza disease. They, as had others before them, notably Rivers, noted that most disease occurred in very young children, primarily between approximately three months and three years of age, with the peak incidence of disease occurring at around ten months.

Very little disease was seen past three years of age, and essentially none past eight years -- six years. This is the age incidence of disease. There's no disease in the first three months of life, peaking at around ten months of age, declining rapidly, becoming very little disease past about three years, and here at about seven, eight years, virtually none out.

Very importantly, besides this epidemiology, Fothergill and Wright also noted that the incidence of disease at any age was inversely proportional to the bactericidal power of the blood. Protection against disease was thus linked to levels

of serum antibodies, passively acquired, maternal antibodies during the first three months of life, and naturally acquired antibodies in the later years, and there will probably be some discussion later on about the origin of these naturally acquired antibodies, but they were not from getting disease and surviving.

And this is the curve of the bactericidal power of the blood, and you can see it's the mirror of the incidence of disease.

It's very interesting to point out that no disease is observed in adults at a point where the bactericidal power of the blood is such that about three times ten to the seven organisms are killed by one mL of the blood. I think this may be one of the first correlates of protection seen for Haemophilus disease.

And I am sure that others will have considerably more to say about this important and insightful study by Fothergill and Wright, and these observations have been repeated and mirrored in a number of studies since that time.

We're here today to discuss the levels of antibodies to be more quantitative that are needed for protection, and some of the subtleties of the immune response that the conjugate vaccines may engender,

subtleties arising from their T cell dependence.

Please allow me now to be specific and go over some of the issues that we would like you to discuss today. I present these questions now to help orient some of the thoughts during the talks that will be presented this morning and early this afternoon to get -- to prime us, as it were, for the -- for the panel discussion later this afternoon.

First, we would like you to discuss and comment on the currently used correlates of immunity, the antibody concentrations, and the percentage [illegible] responders at these concentrations.

If I could have the next overhead.

We would also like discussion and comments on the clinical significance of the reduced Hib responses that have been reported with several of the DTaP Hib combination vaccines, and some of this [illegible] was presented to you in the briefing packages and will be discussed during the presentations today.

Next.

Moreover, we would ask that you consider the contribution of the following -- in fact, this will be the next one -- if we can consider the contribution of the following factors to Hib vaccine efficacy.

The first, a demonstration of immunological memory priming. How important is this in protection of the individual child?

(b) We'd like to discuss the qualify of the antibody response, such as the isotype and avidity in addition to simply the total amount of antibody.

Also we would like to you to consider the effects of a reduction in carriage. In reduction in carriage will have an effect on disease transmission. There will be a herd immunity, and this effect will be particularly to those who were not vaccinated and to those who were vaccinated and did not respond well.

However, we would like you to consider whether this reduction in carriage also has an effect on the individual or does the reduction only occur well past the point where the individual child has been protected.

Additionally, we would ask you to discuss and consider the differences that have been observed in comparative trials of separately administered and combination vaccines in light of the range of responses that have been seen historically with existing Hib conjugate vaccines.

In other words, for some vaccines where we have seen a reduction, how do these reductions, the

lower titres compare to vaccines that we have evaluated historically in clinical trials?

Next, we'd like also for you to consider in your discussion of Hib correlates the relevance of post marketing data that have been obtained, for example, some of the studies, the follow-up studies that have taken place in Europe, in the U.K. and Germany, and we have invited speakers here to discuss some of these.

And we'd like you to also consider the utility and need for post marketing surveillance studies of some of these combination vaccines if they are approved with reduced titres.

And finally, we would like the panel to address other issues that they consider significant, and I guess I should add "and are related to Hib conjugate vaccines."

(Laughter.)

DR. EGAN: There are many significant issues that I think many of you would like to discuss for the FDA, but I would like to keep the discussion to the Hib conjugates.

Before I turn the meeting over to our distinguished Chair, Dr. Greenberg, let me again extend CBER's and OVRR's appreciation to all of you

who have given generously of your time and effort to participate in today's discussion.

As I look around I see an amazing collection of talent that's assembled for this issue, talent that's been involved in the discovery of these vaccines, the development of these vaccines, the use and improvement of these vaccines.

So I think we will have a very lively and interesting discussion today.

Dr. Greenberg.

CHAIRMAN GREENBERG: Thank you, Bill. That really did help set the stage. I'm glad you clarified that last point or we really would have had a wide ranging discussion.

Is John Robbins here?

PARTICIPANT: Yes, he is. Right over there.

CHAIRMAN GREENBERG: Ah, it's been a very long time since I've seen John, and I actually maybe didn't recognize him. Almost 30 years.

DR. ROBBINS: Can I just have the first slide?

I think in any discussion about Haemophilus influenza Type B we should all remember that we're standing on very broad shoulders of people

who did these studies 30 years ago and remind you that Dr. Pittman, Fothergill and Wright, and Patty Alexander were major contributors to our understanding today, and the principles that they proposed in those elegantly written articles stand, have stood the test of time.

Now, how do I go forward?

Bill Egan put up this very important slide. There's a lot to be learned from this slide that was done so many years ago at the Children's Hospital in Boston. As he pointed out, two variables were plotted on one graph. It is the age incidence of the disease and the presence in the general population of bactericidal antibody.

Let me just focus on two aspects of this important relation shown so many years ago. The first is that vaccination against Haemophilus influenza Type B has to be completed by about three to five months to be effective, and there's no need to vaccinate adults because they're immune.

Second is that this development of antibodies in the general population which are almost all Type E antibodies, that is, you can absorb most of the activity in most of the serum with a purified polysaccharide. It takes place in large part in the

absence of the homologous organism. This acquisition of age related immunity is due in large part to a continual interaction with nonpathogenic cross-reacting bacteria in the intestinal tract. It occurs in many cases independent of interaction with the homologous organism.

Now, in 1973, my colleague, Dr. Schneerson, and others working in the lab, namely, also Dr. J.C. Parke, tried to figure out what might be a protective level of antibodies to the Haemophilus polysaccharide. In those days we had a radioimmunoassay, but I think the standardization of the assay and its relation to ELISA has been elegantly done by people today, and we can consider the data as comparable.

He looked at the antibody concentration in 422 adult blood volunteers in the Clinical Center of the NIH, 100 pregnant women at term in Jacoby Hospital, Albert Einstein College of Medicine, and adult volunteers prior to immunization.

And the geometric mean was 1.4 micrograms of antibody with this range. Ninety-five percent of the adults had at the Type E levels greater than and since most adults are protected against Haemophilus influenza and since the mechanism

protection is presumed to be serum antibody, then the protective level may be estimated at .04 to .1.

We estimated it in another way, and that is to take advantage of the remarkable therapeutic success of passive immunization with pooled immunoglobulin when administered to patients, especially boys, with x-linked hypogammaglobulinemia.

We checked 86 immunoglobulin lots, commercial immunoglobulin lots throughout the country. We calculated the catabolic rate of immunoglobulin with a half-life of about 20 days. The recommended dose for hypogammaglobulin patients was .05 to .1 mL per kilogram every three weeks, and the residual or protective level of antibody prior to the next injection ranged from about .12 to .24.

So on the basis of these two studies, we estimated the protective level to be .15 micrograms per milliliter, and the studies by George Siber and his group with Bea Pig (phonetic) come to the same conclusion, that the level of antibody prior to the next injection that was associated with protection was about .15 micrograms of antibody per milliliter. If anything, I think this is slightly high.

About ten years later, Dr. Kayhty and her collaborators in Finland reviewed their data with the

polysaccharide that was shown to be effective in children from about 18 months to 24 months of age, and they concluded that an antibody level of one microgram per milliliter correlated better with protection than the level of .15.

But as Porter Anderson showed several months later actually what they were looking at is this. They took a level of antibody about three to four weeks after immunization, and it was one microgram per milliliter in the post immunization level that correlated best with protection over the following year, although the level of antibody had fallen, yet these people were still protected.

So I think the level of one as proposed by Dr. Kayhty and her colleagues, I think, can be, I think, considered only in light of post immunization levels in two year old children.

Note in two year old children the level of antibody is already starting to rise as the incidence of disease declines and the level of natural antibody increases.

Now, I want to make an important point here. These are children in Gunterberg, Sweden who were injected at three, five, and 12 months, with one injection of Haemophilus tetanus toxoid. This was

material we made years ago of what was followed in most part by Pasteur Merieux, and then the children examined six years later.

Now, note that the control level of antibody is 1.32. It ranges such that about 13 percent of the children do not have levels exceeding .15. So this is development of natural immunity.

Among the vaccinees, both vaccinees had higher levels than the controls. You can see the levels of antibody about one month after the last injection here was about ten. So the levels had declined, but were different, and this was even statistically significantly different.

Among these groups only three percent had less than .15. In other words, at six years of age the effective vaccination at infancy with three injections is to reduce the number of people with less than what you would call protective level.

Let me make a point here. You see, we use two doses of vaccine, 15 and 7.5 micrograms based upon its polysaccharide content, and there's a difference. That is, the higher the dose, the higher the level at six years of age.

I think this must be taken into consideration when the dosage of vaccine is looked at,

that the levels soon after immunization should also be evaluated in how long they last, and I think you'll find that the lower the level of vaccine with three injections at least, the lower the level several years later.

Both, of course, are highly protective. With a fourth injection this is probably mute.

Now, as Haemophilus influenza Type E conjugates were started to be used in the United States, the level of cases declined quite rapidly, but the level, that is, the decline could not be explained on a one-to-one ratio with the percentage of the children vaccinated.

In other words, you were starting to have a decrease in cases in unvaccinated children, so-called herd immunity.

Now, in Finland where epiglottitis is almost as common as meningitis in children and occurs in adults, they notice that as soon as vaccination started, adults who got Haemophilus influenza Type B epiglottis had epiglottis continually due to other causes, but not Type B, not Type B.

In other words, vaccination of children eliminated Haemophilus disease in adults, and to me that's a good clue. It's something that can be

followed accurately.

What happens to Haemophilus influenza Type B meningitis in the United States in the non-vaccinated population, which are adults, and epiglottitis does occur. It's quite dramatic when it's observed, and it could be monitored in three or four hospitals in the United States to make sure that if we have any changes in formulation or anything happens or something is happening to the acquisition of natural antibody, we might pick it up very early by looking at the return of this pathogen as a cause of systemic infection in adults.

Now, I know you all know this, but if you look at the antibody levels of adults, two years olds, and two month olds, you can see that there's a decline that's age related in both pre or so-called natural antibody and post immunization levels.

But at two years of age, antibodies are now appearing when polysaccharide is injected, whereas it does not appear in the infant age group, and I think the best explanation for this, although we haven't got a good cellular basis for saying this, is that there is a gradual acquisition of T cell sensitization or immunity to the polysaccharide that is induced by bacteria in the intestine and the

pharynx, so-called memory component.

Memory was first proposed -- I think it was first -- by a group out in St. Louis in which they showed that children who had been injected with conjugates make a much better response to the polysaccharide when injected at two years of age, and this was called "priming," although priming really in this case should be left to the original definition by -- I got his name now -- from Scotland who proposed that this was a carrier effect upon T cells.

Now, in thinking about what would be an acceptable level of antibody, it's been published in the literature even most recently by a very elegant article on combination vaccines by Dr. Eskola and his associates that the word "memory" could be a surrogate for immunity.

I have a lot of difficulty with that. I think it's speculation because how would you define memory as being protective unless you could follow children that had less than protective levels of antibody and showed that they didn't get meningitis when they were exposed to the organism.

Well, you can see from the experiment that I set up it's not possible, but what Dr. Anderson and his associated did was look at the level of antibody

several days after admission to the hospital of children with meningitis at various ages.

Please bear with me. These are young children. This is two months to 11 months of age, and this is the admission antibody. You can see barely at the level of detection, and these are antibodies in sera posted mission. So you can see that in the group there are very low responses, which has been reported by several groups, except in two children where you had a very brisk, high level of antibody that appeared very quickly after vaccination.

Now, if you look at older children who get meningitis, you can see most of them have barely detectable levels in serum. They had very low levels, but you can see that they respond very quickly, but almost all of them with high levels of antibody soon after admission to the hospital.

And just reviewing Dr. Anderson's data, looking at the patients whose serum was available for the study, as you can see, the older the children, the quicker and higher the antibody response. And what Dr. Anderson and his colleagues said, so natural memory, if you can use these expression, had no effect on preventing meningitis in these children.

And for that reason I urge that when

surveillance is conducted that a good correlate of protection is still .15 micrograms of antibody per milliliter; that the surveillance should be conducted in vaccinees and children and individuals of all ages; that the absence of a protective level doesn't mean that the child gets meningitis because the incidence of the disease is affected by the widespread vaccination that eliminates the organism just about in the population. So that although the children may not have protective levels, they're not exposed.

So, therefore, if you have many children that do not have protective levels, it doesn't mean that they're not susceptible. It probably means that they're not exposed.

We can learn from looking at the experience of other capsulated bacterial pathogens because I think the rules are the same. With meningococcus, they have a polysaccharide. The polysaccharide protects the bacteria against complement. Serum antibodies to the polysaccharide protect, et cetera.

But we have the advantage with meningococcus that we could work with enclosed populations of individuals for a period of time, and I would like to refer you to the elegant article by

Dr. Goldschneider, Gotschlich and Artenstein many years ago in which they looked at the incidence of disease in recruits to Fort Dix with two variables, those who had bactericidal antibody and those who had an organism in the throat.

And when these two factors are put together, you can see you can predict who's going to get meningitis with pretty close to a 50 percent accuracy.

That means if you didn't have preexisting antibody, you were susceptible, and when they vaccinated with the polysaccharide, a key independent antigen, no memory. They had almost 100 percent protection, indicating that these people who did not have bactericidal antibody were capable of making antibody when stimulated with the T cell independent antigen.

There is no evidence of memory in this study. There is evidence for the protective effect of preexisting antibody.

Let me make another point. I think this is overlooked very often. There is no linear correlation between the level of bactericidal antibody and protection. If you have a certain level, you're protected. That's called a threshold phenomenon, and

I'm sure that it obtains for Haemophilus Type B also.

Let me make one other point about carriage. This is from the meningitis Group A in Finland in army recruits. The article is by Dr. Sivonen, and what I want to point out is this. You see, when you look at carriage of the meningococcus in Finnish recruits up to four weeks after they were vaccinated, you could see no effect upon vaccination with meningococcus Group A. Vaccination and serum antibody does not cure established carriage, does not cure it. It's probably quantitative.

But as you started to look later, two months, three months after vaccination, now you can see there is a statistically significant reduction in carriage. It inhibits the acquisition of carriage. It's not 100 percent. It does not cure established carriage.

Well, the questions posed by Dr. -- to patient. When you get my age you'll start doing this, too -- are unanswerable in precise terms, but I would like to point out that you can feed cross-reacting bacteria to adults that have quite high levels of antibody to Haemophilus influenza Type B.

In this slide we just looked at bactericidal antibody, but as I told you, it's almost

all Type B antibody, and if you feed the organism at ten to the seventh, ten to the eighth, the recipients make quite nice levels of antibodies that are specific to the Haemophilus polysaccharide.

So I think that it will be unlikely that vaccination will interfere with the acquisition of natural immunity, but it should be looked for by measuring antibodies in the entire population, and it might be helpful to look in central hospitals for incidence of meningitis in adults, especially epiglottitis.

I think I'll call it quits.

CHAIRMAN GREENBERG: Thank you very much, Dr. Robbins, for a terrific review.

We have a little bit of time for a question. Dixie, I'll get you. Just I'm going to take the prerogative of the chair because this is not my field.

Epiglottitis and meningitis you mentioned as two. Are both of those indicators in adults that could be used to look at population immunity?

DR. ROBBINS: Yes. In children, almost all cases of epiglottitis are caused by Type B. In adults in various parts of the world, there are other causes, other bacteria isolated from the blood, but in

Finland where they have a fair number of cases relative to other countries, Type B as a cause of the disease disappeared as soon as vaccination began.

So if vaccination was no longer inducing herd immunity, that is, eliminating the organism, then we could expect that it might show up quickly in looking at adult cases, including epiglottitis.

CHAIRMAN GREENBERG: And meningitis there, is that going to be in -- no.

DR. ROBBINS: Harry, in New York City when we started to work on this, the leading cause of bacterial meningitis of all ages in the city was Haemophilus Type B. It was the leading cause of adult meningitis.

CHAIRMAN GREENBERG: Okay. Thank you.

Dixie.

DR. SNIDER: John, in talking about immune responses and antibody levels, were you generally talking about anti-PRP or are we talking about something more crudely measured in earlier studies? Could you characterize?

DR. ROBBINS: It's only about -- PRP is an acronym. It's not a very accurate acronym or good acronym, but it's an acronym and everyone uses it, although I prefer the capsule polysaccharide of

Haemophilus influenza Type B, but that's what we're talking about.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: I'd like to have one clarification at least to myself. You briefly touched on antibody levels versus antiviral responses. If a child has a pre-immunization antibody level of, let's say, .1 and then receives vaccines and post immunization antibody level stays same, and certainly that is a concern, but what about child whose pre-immunization level is undetectable and responded to the level of .1/

DR. ROBBINS: I'm not sure I understood your question, but vaccination of infants with the conjugate induces protective level of antibodies in almost everyone. If you examine the height of antibody to the polysaccharide in older children and adults, the pre and post immunization levels are roughly correlated.

That is, the higher the pre level, the higher the post level. It's not a linear correlation that is statistically significant.

This seems not to be an important factor in using conjugates in infants, especially the four injections.

CHAIRMAN GREENBERG: Dr. Edwards and then Dr. Kohl.

DR. EDWARDS: John, in terms of once a child is colonized, how long do you think, in general, that a child would have to respond to that colonization before disease may, indeed, occur?

DR. ROBBINS: You can't find it in the literature. Now, I'm getting a little old. I'm more forgetful than I was, but I couldn't find it, except one article, and that's in one patient, and that is a case in a nursery right in Washington air. We had three cases of meningitis in several days. We wrote about it many years ago.

Two of the cases -- one of the cases was negative before the child acquired meningitis, and that was two days later. It must be very fast. I think once colonization is established, the children are immune.

Now, what is the colonization rate in adults? There's just one -- there are two things I'd like to say. One is it's a rare phenomenon. How rare? I can't answer you.

Where it's been studied, parents or close contacts of a child who is colonized but not sick rarely become colonized. Parents or siblings of a

case of meningitis invariably become colonized, and some of it may last a long time. Sally Sell did that many years ago.

CHAIRMAN GREENBERG: We have time for one or two more questions.

Dr. Kohl.

DR. KOHL: Before the question, I think we should recognize the remarkable achievement in the almost completely wiping out of Haemophilus influenza disease in infants in this country. We kind of gloss over that almost, but I think we should sing the praises of many of the people in this audience who have helped achieve that really remarkable event.

The question to you: later on we're going to hear that there's been reduction of H. flu disease in older children even though there's been a decline in antibody or at least they don't maintain the so-called protective level, and I gather from what you're saying your feeling is that's all basically herd immunity. That's not their own protective immunity.

DR. ROBBINS: There's one good study. I have the slide. It's not important, but I'm sure everyone knows it, by Takula (phonetic) in which they found that if you vaccinated with the conjugates, there were no colonization among 80 children, whereas

the colonization rate in nonvaccinated was about two or three percent. It was 14 versus zero. Have I got that right? Not so bad.

I think they were lucky although they were correct. That is, vaccination with conjugates does not eliminate inhibition of colonization. It reduces it so that the effect is seen in the population gradually, that is, with reduced transmission and increased immunization. The chances of a child transmitting the organism to a susceptible go down and down.

When this was done in Romania with diphtheria toxoid many years ago, about the time you vaccinated 40 to 50 percent of the population, there were no more cases, although the organism remained in the community or in the country for several years afterwards.

In the Gambia, where they vaccinated 40 percent of the children with Haemophilus Type B tetanus toxoid conjugate, when the vaccination was complete, that is, when they had vaccinated all of the children at about six or seven months of age that they proposed, the disease disappeared in the controls and in the rest of the population, that is, even in the nonparticipants.

So to be facetious, and I'm being facetious now, if I vaccinated myself with Haemophilus influenza Type B and walked in the middle of China, it would not affect the rate of Haemophilus disease, but if 40 percent of the children were, then you would gradually see the disappearance of the organism in the unvaccinated children, less than the age of complete vaccination and adults.

It's a gradual process. It's a statistically challengeable or analyzed process, but probably what happens is that as you reduce the transmission, you're reducing the cases beyond the percent of children vaccinated.

CHAIRMAN GREENBERG: We have one last question. Dr. Breiman.

DR. BREIMAN: And I have two very concise, succinct questions. Since the protective threshold was identified, we now have a lot more information about quality and functionality of antibodies. Do you have ideas about threshold as it would relate to subclass or avidity or measure of functional quality of antibodies?

That's the first question. Actually let me just slip in the second question, too, to think about, which is I was under the impression that even

in post Hib vaccine era when there's not very much Hib circulating, that there are data suggesting in older children that there's a very high level of vaccine efficacy, older children where you might expect sort of a decay in antibodies.

And so I wondered if you could address that, too.

DR. ROBBINS: There is no decay in older children. It keeps on increasing.

DR. BREIMAN: Even in the absence of circulating Hib?

DR. ROBBINS: That's right because the stimulus is probably not always Hib. The stimulus can be bacteria with similar structural antigens, like the easy one is Eshrekia (phonetic) coli K100. That only differs in the linkage between ribose and ribitol.

Staphylococcus, if you take any staphylococcus and inject it, you'll get bactericidal antibodies to Haemophilus influenza Type B that bind with the polysaccharide, and that's due to the fact that they're so well contained as polyribitol phosphate.

You can do a bacillus subtilus (phonetic), and there are many bacteria that we discovered that will cross-react. We never went into the structure or

analyzed them because we would probably still be doing it after our discovery in 1973. It's a very common cross-reacting antigen.

I believe that's why the age incidence of Haemophilus differs from meningococcus. With Haemophilus almost all of us are immunized by the age of six. With meningococcus, only about 70 percent of us are immunized. We still have 30 percent of the population that are potentially at risk.

Well, let me go back to one point. You should not assume that you've induced immunity in a population where widespread vaccination has occurred because there were no cases in children with less than protective levels of antibody. I think the explanation for that is there is no organism.

CHAIRMAN GREENBERG: Thank you, John.

I wager we're going to hear more on all of these points as it goes on. I'd really like to thank you.

And I'd just like to simply again underline what Dr. Kohl said, that many of the people in this room, including Dr. Robbins, are responsible for a very remarkable decrease in a very important disease, and all of us owe them a debt of gratitude.

We're now going to move on to the

manufacturers' presentations. We have four manufacturers who are going to speak. I've asked them all to try to limit their talks to ten minutes. They all have asked me for a teeny-weeny bit more time, and I'll give it to them, but I would really put about 12 minutes as the outer limit.

So the first manufacturer who's going to speak to us is SmithKline, and that's Dr. -- and excuse me when I get the names wrong. I always do -- Dr. Bogaerts.

(Pause in proceedings.)

CHAIRMAN GREENBERG: The question is: do we count this as their time?

(Laughter.)

CHAIRMAN GREENBERG: There are clearly advantages and disadvantages of 21st Century technology.

I'll give you a few seconds, sir, to set this up, but I'm going to ask: are you rolling?

Rob Breiman asked you, John Robbins, a first question which was: can more precision be brought to the antibody level if you use things such as subclass avidity or other types of assay systems

DR. ROBBINS: Well, I don't know the answer to that. I could talk for about an hour, which

means I really don't know the answer to it.

(Laughter.)

DR. ROBBINS: I'd say this. That if you have an IgG or IG-1 or IG-2 antibody that reacts with the polysaccharide biolysa (phonetic), there's not much more refinement you're going to do to define what a protective level is.

I personally -- this is my prejudice now -- I have the feeling that trying to dwell on that too much is like buying a Rolls Royce to take your garbage out.

(Laughter.)

CHAIRMAN GREENBERG: Is there any way that -- it looks like you may have --

DR. BOGAERTS: I apologize for this delay. We are clearly not in this business. I hope we do our pharmaceuticals and vaccines better.

(Laughter.)

DR. BOGAERTS: Mr. Chairman, on behalf of SmithKline Beecham, I would like to thank CBER for the opportunity to present the SmithKline Beecham experience with our conjugated PRP-T Hib vaccine in B Type combinations.

We have, indeed, taken B Type, known in this country as Infanrix, as the cornerstone for a

family of pediatric combined vaccines, taking into the combination Hib, which is a specific subject for my presentation today, as well as Hepatitis B and inactivated polio vaccine.

This allows us to then bring a family of permutations, B Type, Hepatitis B, B Type IPV, and B Type HPV/IPV. All of these products are 0.5 mL liquid formulations that can be used then to reconstitute the Hib PRP-T conjugate and offering then an additional range of pediatric vaccines.

Both the last vaccines on the left hand and the right hand are of particular importance for the current recommendations of recommended vaccination schedule in this country and are under review by regulatory authorities.

We do have an extensive experience with this family of products going back first to the Infanrix DTaP with more than 26 million doses distributed today.

In addition, we have more than eight million doses of the combined DTaP Hib vaccines already distributed in 28 countries that have registered such a combination to date.

When confronted with the evaluation and the development of this vaccine, we are aware that it

is impossible, especially for the Hib component now, to run new efficacy trials. Therefore, we considered that complying with the criteria proposed by a similar advisory body, committee in 1991, and as listed here, was the way to go.

So in my presentation I will address how we tried to respond to the five bullets that are listed here.

First, comparative immunogenicity versus licensed Hib vaccines;

Antibody persistence till the time of primary -- till the time of booster;

Priming for a subsequent booster to the native polysaccharide, PRP;

Comparison of the quality of the antibody and the subclasses demonstrating the functional capacity of the induced antibody. So this is what we observe typically when we were confronted with the first results of our combinations, and you see here that I will show you geometric mean concentrations and the percentage of responders according to two classical benchmarks as mentioned by the previous speaker of 0.15 micrograms per mL and one microgram per mL for combinations of increasing complexity starting with DTaP Infanrix and always, and the second

line, the corresponding mixture with the PRP-T.

And what you see is that invariably we accuse a lower antibody concentration for the combo as compared to the separate administration. However, when looking at the percentages of responders, we do see a lower percentage for the benchmark greater than or equal to one, but we do see that for 0.15 micrograms per mL, there is no difference between the separate administration or the combined administration of the vaccine components.

So this brings me then to the question already proposed by Dr. Robbins. What is the origin of these benchmarks, 0.15 and one, related classically as presented for short term protection and long term protection?

The benchmarks have been defined and calculated for nonconjugated Hib vaccine. However, and anticipating on the presentation later today by Juhani Eskola, the conjugated Hib vaccines in their efficacy studies demonstrated greater protection than what would have been predicted if we were looking at a percentage of subjects with titres or a concentration greater than one microgram per mL.

Without going into the detail and accusing that this is a busy slide, I just concentrate here on

the studies in Finland, and you see that if we look at the percentages here in yellow of responders with a titre greater than one, it is out of face with the absolute efficacy that was observed in the same individuals.

This is not the case when you look at 0.15 where there is a greater correspondence.

Going back now to the titres that we observed and looking at the second criteria, comparing us to the established Hib vaccines, I present here data from the literature and every dot here on the table illustrates a study group that was published for the four most widely spread Haemophilus vaccine, HbOC, PRP-OMP and PRP-T, and for the sake of completeness, we also added PRP-D that in this country was not licensed for primary vaccination in infants.

And if I add to this now the observations that we have with our DTaP Hib combinations, then you can see that despite there was a lower antibody concentration with respect to the separate administration, we compare favorably to the titres that have been published for those vaccines that have, indeed, allowed us to control Hib invasive disease.

I highlight in particular our hexavalent, which is of great importance for this country, and you

see that we, indeed, look well as compared to the literature data.

This allows me to go from the primary vaccination then into the persistence, which was also the criterion that was required to study. So here we look at two studies among the many we conducted where antibodies were evaluated at 15 to 20 months of age. So this is pre-booster. After a primary immunization with one of the combinations at three, four and five months of age.

Two validated methods with a different cutoff, but both based on RABA illustrate that if you look at the classical 0.15 microgram per mL, you may see that in the mix there is only 64 percent with detectable antibodies, but if you look behind the curtain and you use a cutoff that is actually lower so that it is a more sensitive method, you are able to retrieve a significant part of those subjects that you then could quality as having antibodies, and the importance of that has clearly been indicated by Dr. Robbins.

This allows me to go to the third criterion, and what about the induction of immune memory to plain PRP, which is an established and accepted way for mimicking the contact with the wild

Haemophilus.

So here we took a study among others that we conducted, conducted by Ron Dagan, who I believe is also in the audience, and the primary vaccination was with one of the DTaP combos at two, four, and six months of age, and the plain PRP challenge was given as early as ten months of age. The blood sampling took place ten days later.

Now, to position the PRP response observed at that age, we have to look at the benchmarks that are appropriate, and what you see here is from the literature again in function of age, the increasing antibody response that you see after one dose of plain PRP. For the sake of our study, the benchmarks are the diamonds that are here at month ten.

And if I put the results from the study, then you can see that the response we obtained is way above what we see in unprimed children, therefore indicative of the induction of priming by the primary vaccination they got with the combination.

I will not go into any great detail for the sake of time, but we did look at all of the classical functional tests and also the avidity. We also looked at the maturation so the phenomenon that avidity with time will increase and, therefore, add to

the quality of the antibody.

So we were unable to find any differences between the combined or the separate administration.

Last, but not least, given the fact that our vaccines are, indeed, already widely used, and I specifically refer her to the situation in Germany where you see that in a very short period of time after their introduction, all Hib conjugate vaccines got replaced by DTaP Hib combinations, and you see that the vast majority today of those vaccines are a dose produced by SmithKline Beecham. So we have here a scenario where looking at post marketing surveillance, we will be able to study relevant effectiveness data for all vaccines.

And Dr. Schmitt later in the program will give you all the details on how we were, indeed, able to show that effectiveness was demonstrated.

This allows me to draw some conclusions, again, following the criteria set out by the Advisory Committee in '91, that indeed, comparison of combined vaccines versus the separate administration of their components showed that we have a lower geometric mean concentration and a lower percentage of responders with a titre equal or greater than one microgram.

But we do see that 0.15 micrograms per mL,

there are no differences. The efficacy trials seem to indicate that indeed the 0.15 micrograms per mL is a more sensitive marker for protection. The antibody concentration and potential of responders is furthermore similar to the range that has been published for those vaccines used in this country and others to control HB invasive disease.

We do see that there is a persistence of antibodies and more even if you use a more sensitive method, and we see that induction of memory has taken place as evidenced by an anamnestic response to a challenge with the plain PRP.

The functional capacity and the characteristics of the antibody, including the maturation, are unaltered as compared to the separate administration, and then fortunately we have already data showing that in a population based field effectiveness has been demonstrated.

Thank you very much.

CHAIRMAN GREENBERG: Thank you.

There's a lot to be packed into the next couple of minutes. So I won't be able to take a lot of questions, but I would like to give the panel a chance to ask one or two questions.

Dr. Kohl.

DR. KOHL: In your handout, not the slide handout, but your written handout, Table 4 is opsonic activity of combined versus separate component antibody response, and am I accurate in reading these GMTs as being about half the separate response?

I know later on they're corrected for IG content, but the uncorrected would seem to be what's important, and is it accurate that it's about half the response?

DR. BOGAERTS: I don't have the table in front of me, but may I ask one of our experts who is in the room, Jan Poolman, to address this specifically?

CHAIRMAN GREENBERG: Table 4 is on page 12 of the handout, and I don't want a 15 minute discussion of serology here.

DR. POOLMAN: The answer to this question is pretty simple. The geometric mean opsonic titres, indeed, in the mixed vaccines are lower, but that directly relates to the lower antibody concentrations as measured by RABA.

So the correct way of looking at this is the opsonic activity on the antibody weight basis. So that is the ratio of the opsonic titer divided by the quantity of antibody, and that we have indicated as a

geometric mean ratio in the far right side of the table, and there you see they are the same.

CHAIRMAN GREENBERG: I think most of us got it.

DR. GRIFFIN: With relevance to what Dr. Robbins said earlier, I assume that all the titres that you're giving us are sort of the peak titres after immunization, and do you have any data or knowledge about a year or two, you know, what the decline is and how high antibody titres are in the follow-up of any of these children?

DR. BOGAERTS: Yes. We, indeed, looked most of the time at antibody titres up to the age of booster, and I think I've shown some of the data where we, indeed, see the normal antibody decline.

What we do see is that, especially if we use a more sensitive method, and that refers to the 89 percent and 90 percent that you have seen on the slide, that we do find detectable antibodies in the vast majority of the children at the time of the booster.

CHAIRMAN GREENBERG: I'm just going to follow up on that because this point was not clear to me. When Dr. Robbins talked, and as I read this literature, the one microgram was an acute response,

and then the .15 was sort of after decay, and I couldn't understand from your presentation whether you were now interchanging the acute response of one microgram and .15 as saying, well, we have a higher acute seroresponse rate if we use .15 as the level, which I think changes the meaning of the point.

Since I assume everybody goes down after the first month, I assume the height of that first month is indicative of what you'll have later on.

Dr. Robbins wants to.

DR. ROBBINS: Just to make a point, these levels of antibody were not take that were -- the two methods used to determine the protective level were not taken from vaccinated children. They were taken from adult sera of the general population and from gammaglobulin made from adult sera which was therapeutically effective.

The level of .15 should be considered as protective in any individual at any given time.

CHAIRMAN GREENBERG: Okay. So when you said seroconversion of .15, that's a month after? When was that .15 achieved?

DR. BOGAERTS: The .15 that I referred to was one month of the completion of the primary vaccination.

CHAIRMAN GREENBERG: Okay. I'm sorry, but I am going to need to move on, and we may if we finish, we may be able to revisit this.

We need to pause before the next speaker, pause to have a different lectern. So then we can keep -- we're not pausing. We're going to keep asking questions.

Dr. Ferrieri.

DR. FERRIERI: Well, I don't want this to be a serologic focus at this point either, but in reference to Table 4 from SKV's prepared materials, I would like to emphasize that the geometric mean ratio may be altered. I don't have a statistical analysis of data, but depending on the nature of the vaccine when given as a mixture, there can be greater alteration and depression of the anti-PRP antibody responses.

And so this may emerge later as we examine what is in the mixture, but it's an important point, in my opinion, to keep in mind.

The first half of the data has to do with DTaP with PRP-T mixed or solo or given separately, but when examined with HBV in the combination, there is a difference in the ratios.

CHAIRMAN GREENBERG: Okay. So I'd like to

ask the next speaker, Dr. Ken Guido (phonetic) to come up from Aventis Pasteur.

DR. CALANDRA: I'm Dr. Gary Calandra, Vice President of Clinical Development for Aventis Pasteur, previously known as Pasteur Merieux Connaught.

Thank you very much for the time to present.

I want to present two slides with regard to the background. This is a slide that discusses the positive story that was mentioned earlier about the tremendous decrease in the number of cases with the advent of the Hib vaccines, this the status in '96 and '97.

You can see that approximately 50 percent of the total cases are in infants less than six months of age and 50 percent greater than six months of age, and when you look at that group on the bottom line, 64 percent are due to incomplete vaccination status for which hopefully we all can increase vaccine coverage, and 36 percent had complete vaccinations, however developed disease possibly due to a nonresponder status, possibly due to overwhelming exposure or another category for which we cannot explain.

Next slide.

This is the experience of several vaccines

being used in one high risk area. Prior to the introduction of Hib vaccine and the Native American in Alaska, the peak incidence was four to seven years of age, similar to what Dr. Robbins has shown, 25 to 40 cases per year and a high carriage rate of five percent.

OMBC, PRP or Pedvax Hib was introduced in 1991 and nearly eliminated the disease in Alaska, with one to three cases per year, but interestingly, as observed by investigators in Alaska, had no effect on carriage, which was measured to be in the eight to nine percent.

In 1996, a different vaccine was introduced into this population, replacing Pedvax Hib, and the number of cases increased rather dramatically. The reasons for reemergence of disease is Pedvax Hib did not eliminate carriage, which as Dr. Robbins has pointed out is very important for the population.

Tetramune, on the other hand, possible or probably did not protect against very early Hib disease, i.e., the importance for the individual.

Point out then by the author that both the population and the specific Hib vaccine may be important in the control of Hib disease. The related thought is that an adequate level of antibody at the

time of exposure is important for all segments of a population.

Next slide.

These are combination vaccine products that have been developed by Pasteur Merieux Connaught, now Aventis Pasteur. TriHIBit is licensed for 15 months and older as a booster dose composed of Tripedia used to reconstitute the Hib vaccine ActHIB.

Quadracel is a vaccine which is licensed in Canada, and it is Tripacel, the DT acellular pertussis-5 component vaccine combined with IPV.

Pentacel combines essentially a Tripacel to reconstitute ActHIB or Penta-5 component vaccine.

I will use these vaccines to demonstrate outcomes relative to the present CBER guidelines: first, TriHIBit in toddlers. These infants shown were vaccinated at equal to or greater than 15 months of age with TriHIBit or separate injections, which means Tripedia or DT acellular pertussis-2 component plus ActHIB.

The predose levels, the anti-PRP levels in this group of infants is taken from our package insert, .89 for TriHIBit, 1.15 for separate injections for the Hib component. Again, we're just looking at the Hib component.

And you can see post dose a tremendous increase in titre in both the combined vaccine TriHIBit and separate injections.

Next slide.

This is a study from four sites in the United States with matched infants. These infants received a 2-4-6 injections of TriHIBit or separate components, the separate components in the first column and the TriHIBit in the second column, and you can see with regard to the anti-PRP antibody that the vaccine was significantly different in terms of the Hib response for separate verse combined, that is, a lower response in the combined product, and this would not meet the guidelines as discussed by CBER.

Next slide.

Pentacel experience with regard to the primary series. Remember, again, Pentacel is DT acellular pertussis-5 component IPV and ActHIB in one group that is the Pentacel group compared to at this time not all separate, but Quadracel-ActHIB, and you can see in this with regard to the GMTs that these would meet the guidelines as proposed by the FDA.

This is a licensed product in Canada and is the predominant vaccine used within Canada.

Next slide.

We've shown you with regard to TriHIBit where we did not meet the requirements of CBER for licensure and where the product from Canada, while not presented for licensure in the U.S., does meet the requirements or could meet the requirements.

In general we concur with your CBER definitions for determining the limits for noninferiority and equivalents for GMT and seroconversion, where seroconversion is ten percent the upper limit of the confidence interval, and the GMT as I have on the slide I won't read those numbers. You have read them.

Thank you very much.

CHAIRMAN GREENBERG: Thank you, Dr. Calandra.

We have time for a question or two from the panel. Dr. Fleming.

DR. FLEMING: If we go back to the Alaskan experience, the Pedvax Hib, can you explain the reason why and the clinical relevance of the increase in carriage in '91 to '95?

DR. CALANDRA: I'm not sure I should answer that for Merck, but I'm not sure that it's statistically different between five and 8.3. I don't know the answer to that.

DR. FLEMING: Nevertheless the point estimate is as it is. So you're right. One explanation could be random variability. Another could be a true pattern.

If it is, in fact, a true pattern, can you explain?

DR. CALANDRA: No, I cannot.

CHAIRMAN GREENBERG: Does anybody have an explanation for Dr. Fleming's question?

DR. BUTLER: One comment is the data are really not adequate to say that there was a increase in carriage during that period, and I think that would be a very large leap, in some areas extrapolating from limited data and in other areas no data to say that.

CHAIRMAN GREENBERG: Any other --

DR. FLEMING: Just to expand on this, would you have expected a decrease in the carriage with such an effective vaccine?

DR. CALANDRA: It expected a decrease in carriage would have been found. It was a surprise that there was no change in carriage. It was not interpreted at the time. It is still not interpreted as an increase, just no decrease.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Gary, your company agrees that

in the TriHIBit experience the immune response that are combined at 4.3 is less than the separate at 7.0. The immune response to Pentacel and Quadracel in your next to the last slide, at least the GMTs are closer to the combined in that previous study than they are to the separate.

Is it fair to compare those studies or they're just so different that it's --

DR. CALANDRA: I would not compare the studies. The Pentacel is entirely Canadian population, Canadian practices, although 2-4-6 and the TriHIBit is totally U.S.

CHAIRMAN GREENBERG: Okay. One last question. Dr. Kim.

DR. KIM: This is a follow-up to the question being asked earlier about Alaska. Is there anyone, Gary, you or anyone in the audience have information on anybody's levels and responses in Alaskan children to PRP-OMP, whether their dose levels were comparable to non-Alaskan population in U.S.?

DR. CALANDRA: I think I will let the Merck people in the audience answer that question. I know the answer, but I think it should be them.

CHAIRMAN GREENBERG: Does somebody have an answer directly to that? Can whoever has the answer

get up and go to a microphone and introduce themselves?

DR. BOSLEGO: John Boslego, Merck.

In general the antibody responses in Alaskan Natives are slightly lower than they are in the general U.S. population.

Okay. We are now going to move on to the third manufacturer, North American Vaccines, and Dr. Helen Cicirello or Dr. Peter Fusco is who I have down.

DR. CICIRELLO: Thank you very much for allowing North American Vaccines to present their experience with evaluation of Hib antibody response when Hib vaccines are used and compared to combination or when they are injected separately.

I will begin my presentation by briefly reviewing two studies in human clinical trials where we have looked at the Hib antibody response, when we have used North American's DTaP vaccine and used other manufacturers which have vaccines commercially available currently.

I will then move on to discussions where North American Vaccines' approach to the -- our knowledge of the fact that a reduced Hib antibody response has been noted and is seen when Hib is used in combination with other current pediatric vaccines

And then I will conclude my discussion by bringing you up to date on where we stand on the introduction of our newly developed Hib conjugate vaccine in human clinical trials.

The first two studies that I will briefly review are use of our, North American Vaccines' DTaP vaccine either alone or in combination with other currently available Hib vaccines by other manufacturers.

The first study is one in which actually Hib vaccine was separated concomitantly, but as separate injections with either acellular pertussis vaccine of North American Vaccine or DT whole cell pertussis vaccine.

And then the second study I will be referring to is the use of North American's DTaP-IP vaccine when it was used to reconstitute at Hib, and in that study the infants received either the one injection where the combination was administered or two separate injections.

The first study took place in the United States and received immunizations at two, four, and six months of age with a serology obtained one month following the third dose, and again, these were infants who received Hib vaccine from the manufacturer

and the DTaP vaccine that was received was either North American's DTaP or whole cell pertussis containing vaccine.

And in that study there were no significant differences observed in the geometric mean titres or in the percentage of subjects who achieved the short term and long term protective threshold level.

The second study was conducted in Sweden where their immunization schedule of infants is at three, five, and 12 months of age, and serology was obtained one month later following the third dose.

Again, in this study there were no significant differences observed in the number and percentage of subjects with anti-PRP-T titres of the long term or short term protection levels. However, there were significant differences in the overall geometric mean titres for Hib in the group of individuals who received the combination vaccine compared to the separate injections.

The individual numbers for that study are as follows. We had approximately the same number of individuals in each study, 189 versus 185. The left most column represents the vaccine in which the children received everything together in one syringe.

We used our DTaP-IPV to reconstitute our Hib.

And the second -- can that be focused a little bit? -- the second column represents the results when children received separate but concomitant immunizations, and you could see that there was a significantly different overall response in the geometric mean titre between individuals in the two different groups either using a Hib antibody assay of the RIA or the ELISA.

North American's approach to this lowering of the overall antibody response for Hib has been the development of a new combination conjugate vaccine, and what we are currently using is a novel carrier protein, rPorB as our carrier.

The following two slides will review some pre-clinical data of the use of this vaccine in comparison to other commercially available Hib vaccines.

This is a preclinical study that was conducted in rats. Five different groups of rats received one of five vaccines. There were two research lots of our Hib rPorB conjugate vaccine.

We also immunized another group of rats with our own Hib-TT vaccine, and then a fourth and fifth group of rats received commercially available

HbOC or PRP-T.

The animals received three immunizations. They had blood draws at each time of immunization, and then received blood draws approximately ten days after each booster vaccination. The boosters occurred about three to four weeks apart.

As you can see from this graph, I want to point out to you that the Y axis represents the ELISA IgG titre, and it is on a log scale. The overall geometric mean titre for those rats who received our new Hib conjugate vaccine using the novel carrier protein are many-fold higher, anywhere from 60 to 100-fold higher than the geometric mean titres that were observed when rats received either our Hib-TT vaccine or the commercially available products.

Now, this is just Hib alone, not in combination with any other vaccines.

Oops, sorry. I went the wrong way.

In a second study done in rats, we see the effect of the combination Hib DTaP-IPV vaccine administered to rats compared to just Hib alone, and in this study, again, we looked at rats who received our Hib conjugate vaccine or those who received another commercially available product.

We can see that when the vaccine was

combined with DTaP-IPV there is a difference in the overall geometric mean titre for the HIB IGG. However, the differences between and the geometric mean titre among those rats who received Hib either alone or -- our Hib either alone or in combination are several-fold higher than those rats who received the commercially available PRP-T vaccine either alone or in combination.

The number of rats who are immunized here are small, and our confidence intervals are quite wide, and I think that's contributing to the reason why there are really no significant differences observed when we looked at the Hib antibody response, either in combination or alone.

We have subsequently gone on to immunize humans with our Hib conjugate vaccine. We have recently concluded a Phase 1 study in adults in which 52 adults have been vaccinated. The vaccine was well tolerated, and the serology is currently in the laboratory being assayed for the Hib immune response.

Our plans are to pursue additional studies in the near future with our Hib conjugate vaccine. Our next population will be in toddlers where we will be immunizing them and comparing them with a commercially available Hib product, and so on

thereafter to follow, we will be putting our Hib conjugate vaccine into combination with DTaP and IPV and evaluating that product in both infants and toddlers.

Thank you very much.

CHAIRMAN GREENBERG: Thank you.

There is going to be one other manufacturer who may wish to speak. So I only want one or two questions.

Any questions? Dr. Edwards.

DR. EDWARDS: Is there any immunogenicity to the Por and B against mening. B disease?

DR. CICIRELLO: Milan, can you answer that?

PARTICIPANT: Not that we can see.

CHAIRMAN GREENBERG: The answer was "not that we can see."

You don't have a glimmer of information about people? I always hate it when I see tests pending.

DR. CICIRELLO: Oh, no. I'm sorry. Well, Mike Pichichero is in the audience here. It's being done in his lab, and I don't know if he has any information.

CHAIRMAN GREENBERG: I've made a living of

showing increased immunogenicity in rodents.

(Laughter.)

CHAIRMAN GREENBERG: Unfortunately it's not that useful. So there's no data?

DR. CICIRELLO: Not yet that we have in our hands.

CHAIRMAN GREENBERG: One last question.

DR. BREIMAN: Are those massive antibody levels functional? Are there measures at all that you've done of opsinophagacytosis (phonetic) or avidity or anything?

DR. CICIRELLO: Milen, do you know if we have any functional body assay results in the animals?

PARTICIPANT: (Inaudible.)

DR. CICIRELLO: Please use the microphone.

CHAIRMAN GREENBERG: But the answer was the antibodies are functional by killing assays.

I'd like to move on now to Wyeth Lederle, and Dr. George Siber is going to present.

DR. SIBER: Good morning. My name is George Siber. I'm Senior Vice President and Chief Scientific Office of Wyeth Lederle Vaccines.

I'd like to say up front that the question of licensing DTaP-Hib combinations or other Hib combinations is a very complex and difficult decision.

There are important scientific and public health reasons to be concerned about introducing vaccines with lower immunogenicity for Hib.

If I could have the first slide, I guess I can control this myself here.

I'll discuss four questions that are relevant to the introduction of DTaP-Hib vaccine and other Hib combinations in the future.

First, is one microgram per mL the protective antibody concentration after a primary series of conjugate?

Second, is priming protective?

Third, will we see an increase in invasive Hib disease if vaccines with lower immunogenicity are widely used in the U.S.?

And if so, do we need to make this decision now or take this risk now?

There are two answers to the first question, and they've sort of been covered already. Yes, a microgram per mL is probably the correct protective estimate for PRP polysaccharide vaccine. This estimate is based on the Finnish studies of PRP vaccine where 90 percent of vaccine recipients were protected, achieved this concentration and only 20 percent of controls did.

The second answer is, no, one microgram is almost certainly higher than the minimum protective level required for protection after conjugate vaccine. A substantial proportion of infants ranging from perhaps five to 30 percent do not achieve this level, and yet almost all of them are protected.

I've not seen data that allows estimation of a protective concentration using the population based method, but I venture to guess that it would be very low, perhaps in the order of .15 microgram per mL.

The second question is whether immunologic priming protects against Hib disease. Before discussing this, let me define priming as the rapid rise in antibody to a protective level in response to natural Hib exposure, which we think is most likely a PRP polysaccharide exposure by the nasopharyngeal route, in other words, colonization.

I'd like to emphasize that we cannot apply the concept of an anamnestic response to proteins to, quote, priming to polysaccharides. For a protein, a rise of antibody within seven days is not observed after the first exposure, but is the key feature, the diagnostic feature of an anamnestic response to the second exposure.

By contrast, with polysaccharides antibody rises, if they occur at all, always occur by four to seven days. Although only a few studies have looked at early responses to polysaccharides, all have shown identical kinetics, a slight fall in three days followed by a rapid rise between four and seven days to peak levels by seven to ten days.

This is true for older individuals given their first dose of PRP, for toddlers given their first dose of conjugate, and for toddlers given PRP after a primary dose series of conjugates. Therefore, it is the magnitude and not the kinetics of the antibody response to polysaccharide that defines what we call priming.

Is priming protective? Again, there are probably two answers to this question. Yes, I believe that priming usually protects. One can infer this from the observation that a substantial proportion of children have antibody declines to less than microgram per mL prior to booster dosing. This was true certainly for the PRP-D studies. It was true of the Hib OMP studies on the Native Navajo, and yet they were protected.

Also in some countries, such as the U.K., where boosters are not given, this proportion may

become quite large, although I don't have direct data on that.

Nevertheless, these children remain primed and almost all appear to be protected.

The second answer is no. Priming does not always protect, and the hypothetical reason is that the interval between exposure to the organism and invasion may simply be too short, less than four days, for an antibody response to occur.

The likelihood of rapid invasion may depend on the organism, the type of exposure, and host susceptibility factors. Based on their tendency to cause outbreaks and the timing of the secondary cases, I would speculate that rapid invasion is most likely with the meningococcus and immediate with Hib and least likely for the pneumococcus.

If this is correct, it follows that the presence of preexisting antibodies at the time of exposure is most important for the meningococcus and least important for the pneumococcus.

Evidence that priming for a rapid response is not always protective includes the following.

First, that breakthrough cases do occur rarely in fully conjugate immunized children who have presumably been primed, and we can see this in the

U.S. About a third of the breakthroughs that are observed are in apparently fully immunized children.

Second, that vaccine failure rates increase with age in the U.K. where only three doses of Hib conjugates are given at two, three, and four months, very early.

And slide six shows you the U.K. data, and summarizes the number of Hib cases observed in the U.K. compared to the number expected to have occurred based on rates just prior to vaccine introduction.

Note that on the one hand, efficacy remains quite high, even in the third year of age when a substantial proportion of these children are likely to have very low antibody levels.

On the other hand, vaccine failure rates, VF in the far column, increase from about .9 percent in the first year to 5.3 percent in the third year presumably due to failure of priming alone to fully protect.

A third bit of evidence comes from pre-vaccine era studies that I think John Robbins just showed you when older children who are capable of responding to PRP quickly still got meningitis, albeit at a much lower rate.

And the next slide shows you unpublished

data from Porter Anderson and David Ingram that demonstrate eight children older than 30 months admitted with meningitis to Boston Children's Hospital. Seven of the eight were able to mount a rapid and high anti-PRP response in the first three days, shown in yellow there, after admission.

One might infer that these children were primed to respond naturally, but developed meningitis anyway.

Finally, I want to emphasize one additional point on priming, which is that effectiveness of immunologic priming can vary. The best predictor we have found of the level of priming is actually the concentration of antibody after the third dose, which correlates well with the response to a toddler booster dose.

And this shows you on the horizontal axis the antibody concentration after the third dose and then the concentration after the toddler booster, and the R value is .71 for those of you who can't read that, highly significant R value.

And the vaccines used here are HbOC alone, with DTP, or with DTaP. So this suggests that vaccines with lower responses after primary immunization will also produce less effective priming.

The next question is whether invasive disease will increase if vaccines with lower immunogenicity are widely used in the U.S., and considering this question, I'd like to make several points as background points.

First, the published immunogenicity study with each of the Hib conjugate vaccines shows substantial variation over about a tenfold range in geometric mean antibody concentration, and Yuhani (phonetic) kindly shared this slide with me from his recent review in Lancet, and what you can see is the average, the tenfold range is in variations roughly for each of the vaccines, and the average GMC of HbOC and PRP-T here is about five micrograms per mL, and all of the studies are above a microgram per mL.

The average GMC for PRP-OMP is about 2.5 microgram per mL, and for the DTaP-Hib combination vaccine, about two microgram per mL, with a number of studies selling GMCs below a microgram per mL.

The second background point is that vaccine responses will be even more variable in practical use than in these tightly controlled clinical studies. This is due to more variation in the timing of doses, incomplete immunization, and lower responses in high risk groups.

Third, in some areas of the country and among certain groups, immunization rates are very low.

Fourth, and I think the most important point has to do with the current epidemiologic situation that we're confronting in the United States in considering this decision. We are not asking whether DTaP-Hib combinations would have high levels of efficacy when introduce into an area where no Hib vaccine is in use. There's no question in my mind that they would.

Rather, we are asking what would happen in the U.S. where more immunogenic vaccines have been used for a decade and have reduced Hib disease rates to extraordinarily low levels. This slide shows CDC data from 1994 and 1995 by Dr. Bisgard, who is in the audience, and it shows that there were only about [illegible] invasive Hib cases reported each year in those [illegible] years.

Compared to the pre-vaccine era, this is estimated to be a greater than 99 percent reduction in disease. Even in infants less than six months of age, the reduction has been an astounding 98.5 percent. It seems likely that herd immunity is important in achieving such low disease rates in the very young.

In this situation, a very slight reduction

in efficacy, say, from 99 percent to 98 percent translates into 90 additional cases of invasive Hib disease in the U.S. That's a point I think we need to keep in mind.

So returning to the question of whether Hib is likely to increase in the U.S., it is certain that Hib antibody levels in infants and older children will decline if DTP-Hib combos come into general use.

As a consequence, a larger number of children will have to rely for protection on priming alone rather than priming together with preexisting antibody.

A second consequence is that Hib colonization rates may increase, leading to less herd immunity and an increased risk of Hib exposure for unimmunized, partially immunized, and immunocompromised children.

There is some evidence, though limited, that in animal studies and human studies that higher levels of antibody are required to prevent colonization than to protect from invasive disease. The higher rates in Alaskan infants that we have heard about may be due to the lower antibody response to PRP-OMP, but of course, these populations also differ in other ways.

The final question I'd like to pose is whether we need to make this decision now. That's supposed to be a scale. It doesn't show up very well.

In considering this question, we weigh the magnitude of the risk, lower Hib antibody, and perhaps more Hib disease against the magnitude of the benefit, fewer shots and perhaps higher acceptance and increased vaccine coverage.

On the risk side, will we see more Hib disease? I would answer that we can't really know that for sure, but it is certainly a possibility.

What would the impact of more Hib disease be? Again, it's hard to say, but it would certainly raise concerns about vaccine efficacy. It certainly did that in Alaska.

On the benefit side -- I think I'm missing the benefit slide, but I'll tell you -- on the benefit side of the equation, the benefits of reducing the number of injections include less discomfort for children and parents and convenience for providers.

But from a public health perspective, the main benefit boils down to improved vaccine uptake. I guess we don't know whether compliance would improve further if fewer injections were given, but the potential for improvement may be modest based on the

current very high immunization rates.

Is there another way to reduce the number of injections without the risk? Of course, there are other options. In the near term, DTaP-IPV-HepB combos are likely to become available. These will reduce the number of injections per visit by two.

In the longer term, manufacturers may be able to include Hib with pneumococcal and ultimately meningococcal conjugate vaccines and perhaps avoid or reduce suppression of the Hib response.

So to summarize, I think we have two options. On the one hand, introduce DTaP-Hib combos and perform careful post marketing and surveillance for HIB disease and vaccines failures.

On the other hand, we could achieve a near term reduction in the number of shots with other combos, perhaps obtain more information by comparing vaccine failure rates with currently available vaccine, and maybe we'll hear more about that later, and encourage manufacturers to evaluate other strategies for combing Hib.

Thank you.

CHAIRMAN GREENBERG: Thank you, George.

We're running a little late. What I would like to do is I understand that Merck was in the

audience, may wish to take a few moments; am I correct?

DR. UKWU: Henrietta Ukwu from Merck.

CHAIRMAN GREENBERG: It's not on. Why don't you go up to the podium?

DR. UKWU: It's on now?

CHAIRMAN GREENBERG: That's fine.

DR. UKWU: Okay. Henrietta Ukwu from Merck.

Sine Merck does not have any data on PRP-OMP in combination with DTaP vaccines, we have not prepared a formal presentation. However, we would like to take a few minutes to comment on our understanding of nasal carriage with Hib vaccines in general and Karen Kaplan from Merck will be making those comments.

Karen.

CHAIRMAN GREENBERG: Can you give me a hint on how long your few moments will be?

DR. KAPLAN: Four.

CHAIRMAN GREENBERG: Thank you.

DR. KAPLAN: I'd like to just make a few comments about the issue of Hib carriage. It's clear that there remain gaps in the scientific knowledge base on the subject of carriage. In terms of

interpreting the studies that have been done, there are certainly differences among the populations that have been studied, the high risk versus low risk populations, and one needs to be exceedingly cautious about generalizing the findings from one study to the next.

Furthermore, in many cases the cross-sectional design offers just a single look at what is clearly a dynamic phenomenon. In many of the studies, in most of the studies Hib colony counts are not performed, and in fact, in Marina Barbour's study in the U.K. where she really did look at colony counts, as well as antibody levels, vaccinated carriers had very low colony counts compared to the nonvaccinated carriers, and vaccinated carriers also had the highest antibody levels.

Furthermore, the clinical significance of carriage is still unclear. In fact, the question is: do vaccinated carriers transmit disease as effectively as nonvaccinated carriers do?

Can I have the next slide?

There have been a number of studies that have been done looking at the various Hib conjugates and their effects on carriage, and if you look across the Hib conjugates, some have shown reductions in

carriage. Others have shown persistence in carriage. It's not confined to single conjugate vaccine.

In fact, the studies referred to on this slide have been performed in the so-called low risk populations.

In Finland, there was a reduction in carriage, in Atlanta a reduction in carriage, persistence of carriage, in England and in Chile. In fact, there were 40 percent of PRP-T vaccinees had at least one positive Hib culture done.

The next slide.

PRP, carriage with PRP has been studied exclusively in the high risk populations, and we know that those populations are different both because of who they are and in terms of the pressures for disease transmission that may occur, but certainly in the Navajo there was a reduction in carriage, and among the Native Alaskans there was persistence of carriage demonstrated by Gilil and colleagues.

I think the pre-vaccine era carriage rates are estimated to be around six percent, and I think one can say that their study demonstrated persistence in carriage, although interestingly enough among the Alaskan Natives in the pre-vaccine era, despite astronomically higher rates of disease, their carriage

rates were largely the same as those among the non-high risk populations.

Next slide.

Some conclusions then, some things to think about.

In general, introduction of Hib conjugate vaccines in non-high risk populations have reduced carriage of the organism, but there clearly have been exceptions. Only PRP-OMP has been evaluated in high risk populations for its impact on carriage.

But, in fact, the relative importance of which Hib vaccine you choose and its effect on carriage is not known. It's just not clear.

Next slide.

And, in fact, there is other evidence that does support the fact that PRP does have an effect on herd immunity. In Israel there was a 96 percent decline in invasive Hib disease. That includes a 66 percent decline in infants under three months of age for whom a direct effective vaccine would not be expected.

And in Alaska, there was a marked decline in Hib disease in persons ten years of age and older who were never vaccinated, and the greatest decline was, in fact, seen in the Native Alaskan

subpopulation.

Thanks.

CHAIRMAN GREENBERG: Thank you.

What I'm going to do is first catch up. I forgot -- you'll have to excuse me -- at the very beginning of this session to ask whether there was anybody in the audience that had anything to say in the open public hearing. So I'm going to do that. I'm going to do a catch-up vaccination now and ask whether we have anybody in the audience with something to say.

I'm looking around and don't see it. Ah, yes, I do.

I can't see the slide. Dr. Granoff.

DR. GRANOFF: Don Granoff. I'd like to --

CHAIRMAN GREENBERG: No, I think you're going to talk at the next open public. You can talk now or you can talk then. It's your right, but there's more time probably if you -- okay.

Anyone else? Yes. Oh, you'll also talk at the next open. Yeah, that's fine. We have two open public sessions. So I think we'll save these until the next one.

In which case, I am going to conclude this morning's meeting and let everybody take a break. We

didn't -- I think to some degree, and I'm sure the committee members have other questions for the speakers, and is it okay for them to address them while they have coffee?

It's not. They can't do it. So they should try to keep and get their questions together, and if we can get a little time later on in the program, we'll try to catch up.

Thank you.

I'd like you to be back here at -- you have a ten minute coffee break.

(Whereupon, the foregoing matter went off the record at 10:58 a.m. and went back on the record at 11:13 a.m.)

CHAIRMAN GREENBERG: Okay. We're now going to start with Dr. Peggy Rennels, who's going to talk about the response in a DTaP-Hib vaccine with inactivated polio.

DR. RENNELS: I'll present to you results from a study that demonstrated diminution for the anti-PRP response to a combined DTaP-Hib vaccine by concurrent IPV vaccination, and the collaborators with me on this project were Drs. Englund, Bernstein, Losonsky, Anderson, Pichichero, Munoz and Wolff, and this study will be published in May of 2000 in PIDJ.

The sponsors for the study were the FDA and NIH, and it was carried out through the five NIH supported vaccine treatment and evaluation units located at Maryland, Baylor, Cincinnati, St. Louis, and Rochester.

The rationale for doing this study was that in pre-licensure studies Hib vaccines and acellular DTP vaccines were evaluated with concurrent OPV; that no studies had been published comparing the immune responses to combined Haemophilus and DTaP vaccines when co-administered with IPV versus OPV, and as you're all aware, all IPV is now the standard of care in this country.

I, therefore, designed a study in which children received at two, four, and six months of age one of the three then recommended polio schedules, all OPV, sequential IPV-IPV-OPV or all IPV.

The reference arm, Arm 1, received with the OPV separate injections of DTaP and PRP-T. Arm B received all OPV, but combined DTaP and PRP-5. The other two arms also received the combination vaccine.

I should mention that the same lot of PRP-T was used throughout the study in all arms.

The vaccines that were used were the tripedia DTaP, ActHIB PRP-5. TriHIBit was the

combination. IPV was IPOL. All of these were manufactured and donated for this trial by Aventis Pasteur. Orimune was the Lederle OPV.

I want to point out the injection sites of the IPV and the combined DTAP-Hib were in separate thighs.

The primary objective of this trial was to confirm that the experimental treatment arms were non-inferior to the standard arm with respect to the proportion of children achieving protective levels of antibodies to the polio viruses, tetanus toxin, diphtheria toxin, and Haemophilus, and I'm only going to discuss the Haemophilus results.

The sample size determination for establishing equivalence was based on the proportion of children achieving one microgram or more of anti-PRP. The experimental arm was to be considered to be equivalent to the reference arm if the upper bound of the 95 percent confidence interval for the difference in the proportion of reference arm minus the experimental arm was less than ten percent or if you subtract it the other way around, experimental arm minus reference arm. This would be minus ten percent which is the way the FDA then asked us to calculate it.

The study would have 90 percent power if 95 percent of the children obtained protective levels. That was based on pre-licensure of published studies and turned out to be a bit of a high estimate.

The number of subjects analyzed are shown here. Note that the intent to treat children were those who were enrolled and who had a post dose three serum antibody assay for anti-PRP. So we actually enrolled more children than that.

The protocol children primarily differed from the ITT children in minor deviations from timing of one of the vaccinations or the post dose three lot. There were no important differences between the ITT and protocol group.

Serology originally was planned to be all performed in the laboratory of Dr. Gennie Losonsky at the Center for Vaccine Development, but part way into the trial the FDA requested that all of the anti-PRP assays be done by Connaught by RIA so that the results could be compared to their other trials.

And now the results. A lot of data on these slides. Let me walk you through this first one.

Here are the anti-PRP geometric mean titres for each of the four treatment groups with A being the separately administered DTaP plus PRP-T

given with OPV.

The B also OPV, but this time combined DTaP and PRP-T.

C, combination plus sequential IPV, IPV, OPV.

And D, combination with all IPV, and that's now the standard.

I have put here both the protocol group and the intend to treat group. Here are the 95 percent confidence intervals, and shown here are by an OVA (phonetic) the P values for the differences between various groups.

Now, in order to save time and to simplify it, I'll just talk about the intent to treat differences. A versus B, not significant but borderline. So the two OPV groups were not significantly different, but they were borderline.

Now, when you compare though the OPV in separate group with the IPV containing groups, the differences are highly statistically significant, and although we didn't set the study up to analyze it in this way, if you do compare the combined group who got OPV with the combined groups who got IPV, again, the differences are quite highly significant.

And now here are the proportion of

children achieving greater than or equal to .15 micrograms per mL. The slide is set up in the same way, and similar results. A versus B not significantly different. However, A versus the IPV containing highly significant and B, the combination versus the combinations that contained IPV borderline significant.

The percent achieving one microgram or greater, you can see the differences are increased here as expected. A versus B, again, not significantly different, but A versus C and D, highly significant, and B versus C and D, highly significant.

Now, analyzing it one more way, let's look at the difference in proportions between the reference arm and the experimental arms and between B and the IPV containing arms. First, this is the difference in proportion of children achieving greater than .15 microgram per mL, and here are the 95 percent competence intervals around that, and this column is a proportion, difference and proportion of those achieving 1.0.

Look at the lower confidence bound, lower bound upon that confidence interval, and recall that we defined as equivalent if they had less than a ten percent or a minute ten percent difference of that

lower bound.

And by that, albeit arbitrary definition of equivalence, you can see that the only group that could be considered equivalent to the experimental group was B.

And you could see also that the difference in the proportions went from a minus 4.4 to a high or minus nine for the lower bound to a high of minus 40.

This is the per protocol analysis. There were no differences in that.

The results, overall results by site did not differ, and the sample sizes, however, were inadequate to analyze differences between treatment groups at each site because the sample sizes got as small as 12.

But we concluded that in this trial concurrent IPV interfered with the primary anti-PRP response to this lot of this combination of DTaP-PRP-T.

Now, I wish I could tell you that we did a booster trial, and everybody was primed, and we have great kinetic data. I can't. Unfortunately, we didn't do a booster trial, but when we did become aware that there were 47 children who had post dose three anti-PRP levels of less than or equal to .15, we

attempted to locate those children with the intention of any child who had not yet had a fourth dose booster of giving it and drawing a blood one month later, and those children who had had a fourth dose booster given by their primary care physician, go ahead and draw blood.

We were able to get blood on 43 of those 47 children, but the time period between vaccination and blood drawing varied between one and eight months, making the data difficult to interpret, but I will show it to you.

Another thing I want you as you're looking at the data when we come to the end. Please note that there was a difference in the days from vaccination to the blood drawing in the Maryland site where the Maryland site, the mean and median being three to four times longer, and that is because we enrolled them more quickly so that our children had been boosted sooner, and therefore there was a longer interval between immunization and blood drawing.

And now if I could have the overheads.

The development of my slides was interfered with by an act of nature. So excuse the slightly clumsy presentation.

Here are the geometric mean concentrations

of anti-PRP after dose four plotted by days between vaccination and phlebotomy, and I think you can get the impression that, indeed, the longer from vaccination, the lower the antibody levels, and in fact, the P value by logistic regression was .06.

However, there were post dose four 15 children who had an anti-PRP of less than one microgram per mL.

Next.

And 12 of those 15 with less than one microgram had received one the two IPV containing regimens.

Next.

The vaccine received as the fourth dose are shown here. Each of these dots is one child. You can see there was only one child who had gotten TriHIBit as a booster. There are a few who had gotten HbOC. Most got PRP-T, and the proportion of the children with less than one microgram per mL receiving these vaccines didn't differ from the proportion who had greater than one microgram per mL who received those vaccines.

So I don't think it's a function of what was given as the booster.

Next.

Now, here what bothered me a bit is that ten of those 15 children who had less than one microgram per mL were from my two sites, University of Maryland sites, Annapolis and Frederick, but I think that most of those, probably seven of ten of those can be explained by the long interval between vaccination and blood drawing, and it does appear that at least a few children here were probably not primed, but I think that's all I can say from these data.

That's it.

CHAIRMAN GREENBERG: Thank you, Dr. Rennels.

Thank you also for being a little bit ahead of schedule. We have time for a couple of questions.

Dr. Edwards.

DR. EDWARDS: Petty, the children that are noted who did not appear to be primed, those children that had a phlebotomy after their fourth dose within the one month period of time, is there an opportunity to recall those children to look at their immunoglobulins, to look at other responses to the other vaccines? Maybe you have antibody levels with diphtheria or tetanus.

DR. RENNELS: No, we don't. No, with

those who will didn't respond well to the fourth dose, we simply offered them a free dose of HbOC, and we did not follow up

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: Did you have any subjects from the high risk population in your study?

DR. RENNELS: These were -- well, they were U.S. We eliminated immunocompromised children. There were no American Indians or Alaskan Eskimos.

DR. FAGGETT: Or inner city?

DR. RENNELS: Sure, there were inner city children at some of the sites, un-huh.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: Peggy, can you possibly elaborate the potential mechanisms of interference by IPV?

DR. RENNELS: I was hoping you all would tell me. Well, obviously it's not interference at the draining lymph node because they were given in opposite thighs. The only thing that I can think of is that if you give an IPV, you're giving a sudden massive exposure to antigen to the systemic immune system as opposed to giving OPV where the exposure is to the mucosal immune system and it's delayed and it's slower as opposed to a lot of antigen at the same time

as all the other antigens that are being given.

CHAIRMAN GREENBERG: I'm going to take -- you're not all going to be asked. So I saw Dr. Estes and then Dr. Robbins, and then we're going to call it quits.

DR. ESTES: Do you know was the response to the polio normal?

DR. RENNELS: Can you take the paper off the slide here?

There were certainly differences. Was it normal? Ninety-eight percent of children had neutralizing antibody to serotypes one and two and 92 percent had neutralizing antibody to serotype three, and although that's a bit low, it really didn't differ by treatment group.

CHAIRMAN GREENBERG: Okay. Dr. Robbins.

DR. ROBBINS: How much protein antigen is there in those inactivated polio virus preparations?

DR. RENNELS: I don't know.

CHAIRMAN GREENBERG: Is there anybody who can answer that question? There ought to be in the audience. Micrograms of protein in the IPV preparation?

Well, somebody from FDA should be able to figure that out and give us the answer after lunch.

I will, since lots of this seems to me to turn on numbers in some way or another, I'll leave the last question for Dr. Fleming.

DR. FLEMING: The results that you're presenting are all the levels right after the third dose, correct?

DR. RENNELS: Correct.

DR. FLEMING: And it looks like basically in the presence of the IPV there is at least relative to the FDA criterion a concern, an issue of concern to me that I think it's not just your talk, but across the board is what about after the first and second dose. At least from the epidemiology, as I understand, presented up front, the vast majority of this risk is in the first two years, peaking at nine months, and it looked to me like ten to 15 percent of the incident cases are before six months.

And yet we're achieving 99 percent efficacy. So something -- there's something else going on here.

DR. RENNELS: Actually I have data on post dose two, which I didn't bring, and basically all and I haven't analyzed it, but I can tell you that the immune response after post dose two in all the groups was fairly low.

DR. FLEMING: But was it discernably lower in Group D, i.e., in the combinations with IPV than in Group A?

DR. RENNELS: I don't recall. It's there, and we can look at it.

CHAIRMAN GREENBERG: I'd like to move on to the next speaker, who's Dr. Carol Zenko, and she's going to talk about anti-PRP responses and combined vaccine and variability at different clinical trial sites.

DR. ZENKO: Antibody responses to a combined DTaP-Hib vaccine with OPV or IPV, variability of anti-PRP responses at different geographical sites.

Next.

The primary objective in doing this study was to compare the antibody responses to PRP one month after three doses of a DTaP-PRP-T combination vaccine were given with either OPV or IPV at two and four months of age.

The secondary objective was to evaluate the antibody responses to diphtheria and tetanus toxoids, pertussis antigens, and polio virus.

Next.

Subjects were healthy two month old infants with no prior immunizations. They were

recruited from private pediatric practices in suburban Chicago and New Orleans, and we had originally hoped to enroll 450 subjects in this study.

Next.

Immediately upon enrollment subjects were randomized into one of two groups. Group A received OPV at two and four months. Group B received IPV at two and four months. All subjects received the DTaP-PRP-T combination vaccine at two, four, and six months, as well as a Hepatitis B vaccine at two and four months.

The birth dose of Hepatitis B vaccine was not given. The third dose was scheduled to be given when the subject was 15 months of age. Blood was drawn immediately prior to the first immunization at the two month visit and again at the seven month visit one month after the last immunization at six months.

The DTaP-PRP-T combination vaccine was given in the right thigh. The IPV vaccine was given in the left upper thigh, and the Hepatitis B vaccine was given in the left lower thigh.

The IPV vaccine was IPOL. The DTaP-PRP-T combination vaccine was TriHIBit, and Orimune was the OPV. Hepatitis B was Recombivax.

Next.

We had a provision in the study design for subjects that we termed nonresponders, and these nonresponders were subjects who had these antibody levels at seven months of age.

The non-responders were offered an additional dose of either PRP-T or DTaP vaccine. Blood was drawn immediately prior to the additional dose and again one month after the additional dose.

Next.

While we were still enrolling subjects in this study, on June 16th, 1998, the FDA placed a clinical hold on further enrollment in our study. Preliminary results from a similar study, Peggy's, being conducted at the NIH Vaccine Evaluation Unit suggested interference in the immune response to PRP-T when a DTaP-PRP-T combination vaccine was administered concurrently with IPV.

Subjects who had not received the three DTaP-PRP-T combination vaccines at the time of the clinical hold were allowed to continue on in the study. However, they received the DTaP and PRP-T separately.

Next, please.

At the time of the clinical hold, there were 356 subjects who were enrolled in the study. One