UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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THURSDAY,

MARCH 8, 2001

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The Advisory Committee met in the Versailles Room, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 10:33 a.m., Robert S. Daum, M.D., Acting Chairman, presiding.

PRESENT:

ROBERT S. DAUM, M.D., Acting Chairman

CLAIRE BROOME, M.D.

JAY BUTLER, M.D.

MICHAEL DECKER, M.D.

PAMELA S. DIAZ, M.D., Member

SCOTT EMERSON, M.D., Ph.D.

WALTER L. FAGGETT, M.D., Member

PRESENT (Continued):

LYDIA FALK, Ph.D.

BARBARA LOE FISHER, Member

G. SCOTT GIEBINK, M.D.

JUDITH D. GOLDBERG, Sc.D., Member

DIANE E. GRIFFIN, M.D., Ph.D., Member

SAMUEL L. KATZ, M.D., Member

KWANG SIK KIM, M.D., Member

STEVE KOHL, M.D., Member

CAROLINE HALL, M.D.

RICHARD INSEL, M.D.

DOLORES LIBERA

PAMELA McINNES, D.D.S.

DAVID S. STEPHENS, M.D., Member

MELINDA WHARTON, M.D., M.P.H.

NANCY CHERRY, Executive Secretary

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

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

(10:33 a.m.)

ACTING CHAIRMAN DAUM: I'd like to call the open session, session seven, of our meeting to order, please.

We'll begin by asking each of the committee members seated at the table to introduce themselves, and then we'll turn the floor over to Nancy Cherry for announcements and conflict of interest.

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

DR. STEPHENS: David Stephens, Emory University.

DR. KIM: Kwang Sik Kim from Johns Hopkins.

DR. GRIFFIN: Diane Griffin from Johns Hopkins.

DR. DIAZ: Pam Diaz, Chicago Department of Health.

DR. KATZ: Sam Katz from Duke University.

DR. GOLDBERG: Judy Goldberg, New York University.

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

DR. INSEL: Richard Insel, University of Rochester.

DR. WHARTON: Melinda Wharton, CDC.

MS. BROOME: Claire Broome, CDC.

DR. BUTLER: Jay Butler, CDC.

DR. EMERSON: Scott Emerson, University of Washington.

MS. LIBERA: Dolores Libera, Allergy and Asthma Network, Mothers of Asthmatics.

DR. McINNES: Pamela McInnes, National Institute of Allergy and Infectious Diseases, NIH.

DR. DECKER: Michael Decker, Aventis Pasteur and Vanderbilt University.

DR. GIEBINK: Scott Giebink, University of Minnesota.

ACTING CHAIRMAN DAUM: Thank you.

And I'm Robert Daum from the University of Chicago.

Nancy, you're on.

MS. CHERRY: Okay. Announcement. It was brought to our attention yesterday that it gets pretty noisy in this room. Not only do we have the sounds of construction, but some of you have laptops, and so I would ask that there be a minimum of whispering among the audience members because it makes it hard for

everyone else to hear.

I also would ask a really big favor, and that's that you turn off your cell phones.

I want to call your attention to the front desk that you passed as you came in. If there's anything that we can do to help anyone, contact the FDA staffers at the front desk. Denise Royster is out there. She's the one that has done much of the work to put this meeting together. Also Sheila Langford is out there today.

And now I will read the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with open session of the Vaccines and Related Biological Products Advisory Committee meeting on March 8th, 2001 and is related to the discussions on developing new pneumococcal conjugate vaccines for U.S. licensure.

Committee members Snider and Manley are unable to attend this meeting, but no votes are expected today, and no temporary voting privileges have been extended to any consultants.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reports by meeting

participants. As a result of this review, the following disclosures are being made related to the discussions today.

Drs. Goldberg and Insel have been granted waivers in accordance with 18 USC 208(b)(3), which permits them to participate fully in the discussions.

In addition, Dr. Giebink has been granted a limited waiver which permits him to participate in the discussion by sharing his expertise and experience.

Drs. Broome, Butler, Daum, Goldberg, Griffin, Hall, Kohl, Stephens, and Ms. Libera have associations with firms that could be or appear to be affected by the committee discussions. However, in accordance with 18 USC 208 and Section 2635.502 of the Standards of Conduct, it has been determined that none of these associations is sufficient to warrant the need for a waiver, a written appearance determination or an exclusion.

With regard to FDA's nonvoting invited guests, the agency has determined that the services of Dr. Michael Decker as a non-voting industry representative are essential. He has reported that he is employed by Aventis Pasteur as the Vice President of Medical and Scientific Affairs. He is also a

vaccine researcher who has had previous associations with all U.S. vaccine manufacturers.

In addition, he has a financial interest in a firm that could be affected by the committee's discussions.

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 discussions. Their recusals will be noted for the public record.

With regard to all other meeting participants, we ask in the interest of fairness that you state your name and affiliation and any current or previous financial involvement with any firm whose products you wish to comment on.

Copies of all waivers addressed in this announcement are available by written request from the Freedom of Information Office.

ACTING CHAIRMAN DAUM: Thanks very much, Nancy.

There's one additional clarifying announcement that I would like to make. Yesterday we had one question that was subjected to committee vote. The question was are the available data adequate to

support the efficacy of DTPa-HepB-IPV vaccine when given to infants in a primary series at two, four, and six months of age. The correct committee vote for anyone who came away confused -- I apologize -- was five members voted, yes, they were adequate; six members voted, no, they were not adequate; and one member abstained. I just wanted to clarify that.

Today we turn to the simpler topic of pneumococcal vaccines, and we will begin with calling on Marion Gruber again to give us an overview from the FDA regarding this topic.

DR. GRUBER: Good morning. My name is Marion Gruber. I'm with the FDA Office of Vaccines.

And I would like to welcome the members of the committee and all others to the important topic of strategies for licensure of new pneumococcal conjugate vaccines.

The committee will be asked today to discuss licensure strategies for new pneumococcal conjugate vaccines that are currently in clinical development. The purpose of this presentation is to summarize the various approaches under consideration for U.S. licensure of these new products and to outline the issues that are pertinent to these approaches.

As you know, the Wyeth Lederle subvalent pneumococcal conjugate vaccine Prevnar was licensed by FDA in February of 2000. This vaccine is indicated to protect infants and toddlers against invasive pneumococcal disease that are caused by the seven serotypes contained in that vaccine. And this vaccine is administered as a four dose series.

The prophylactic efficacy of Prevnar against invasive disease was demonstrated in a large field efficacy study conducted in the United States by Northern California Kaiser Permanente Health Care System, and a high level of efficacy in preventing vaccine serotype invasive pneumococcal disease was demonstrated in the primary analysis and was 100 percent.

Efficacy in preventing invasive disease due to all pneumococcal serotypes was 90 percent.

Next slide, please.

Published results by Juan Estola, et al., in the New England Journal of Medicine of the clinical trial of Prevnar in prevention of acute otitis media that was conducted in Finland showed that the efficacy of this vaccine against any cause of acute otitis media was six percent. Efficacy was 34 percent against all pneumococcal acute otitis media, and was

57 percent against vaccine serotype acute otitis media.

And a supplement for an acute otitis media indication for Prevnar is on file with the agency.

Next slide.

In order to increase protection provided by pneumococcal conjugate vaccines to other prevented pneumococci in the United States and worldwide, vaccine manufacturers have generated new pneumococcal conjugate vaccines that contain many more serotypes than those contained in Prevnar.

And these vaccines differ with regard to the polysaccharide antigen concentration, the protein carrier chosen for conjugation, and vaccine valency. Some of these antigens are combined with vaccine antigens directed against non-pneumococcal pathogens, and Phase 1 and 2 clinical studies for these products are either ongoing or have been completed.

CBER has received clinical development plans from vaccine manufacturers for these new pneumococcal conjugate vaccines, and those include alternative approaches for obtaining approval for these products.

And under current considerations are to conduct noninferiority studies based on select immune

parameters for the seven serotypes common to new vaccine in Prevnar; to conduct clinical endpoint efficacy studies for invasive disease endpoints outside the United States; to submit data from completed controlled efficacy trials for acute otitis media endpoints; and to submit data from completed controlled efficacy trials for pneumonia endpoints and/or combination of these elements are also likely. In some cases, more than one vaccine indication may be sought.

If licensure of pneumococcal conjugate vaccine is to be based on noninferiority studies comparing immunologic responses, the parameters which would best predict protection would need to be quantitatively defined.

However, a whole lot of protection against invasive disease could not be derived directly from the efficacy trial for Prevnar due to the paucity of vaccine failures. Therefore, immune parameters that are perhaps less clearly associated with vaccine efficacy may need to be considered.

And very recently, on February the 26th, an FDA-NIAID sponsored workshop has taken place to discuss various immune parameters that could be used to assess noninferiority of vaccine responses, and

thus potentially serve a basis for a head-to-head comparison of new vaccine product to Prevnar, and a synopsis of the outcome of this workshop will be presented to you following this presentation.

Next slide. Thank you.

I'd like to take two minutes to briefly review the regulatory approach that was taken by the center during the licensure process of Prevnar. As you may recall, the Advisory Committee meeting of November '99 was dedicated to the discussion of Prevnar and the results from the manufacturing bridging studies were present.

And this manufacturing bridging study was conducted to perform an immunological bridge between lots that were prepared at commercial scale and to the pilot scale that was used in the efficacy trial.

Anti-pneumococcal responses between groups immunized with vaccine lots prepared at full manufacturing scale compared with those of a group immunized with a single lot prepared at pilot scale, and this comparison was based on the percent of subjects responding with antibody levels above a pre-specified antibody threshold level.

And the chosen threshold to antibody levels provided maximal discrimination between naive

and immunized individuals at seven months of age by determining concentrations where the greatest percentage of immunized individuals were above that threshold and the lowest percentage of naive individuals were above that threshold.

And now I'd like to briefly show you all this using serotype 6B as an example. In the red curve, you see that's the reverse cumulative distribution curve for the immunized population or the immunized group. The green curve then represents the RCD of the unimmunized group, and the black curve is the difference between these groups.

And the antibody threshold level for serotype 6B that maximally discriminated between immunized and unimmunized individuals was .25 microgram per mL.

Now, conceptually the percentage of individuals with sero-responses above threshold antibody concentrations could be considered a criteria for establishing noninferiority based on a head-to-head comparison of a new pneumococcal conjugate vaccine with Prevnar.

And of course, the statistical criteria for comparability to Prevnar would need to be discussed and would need to be defined, and as an

example, criteria that have previously been used for determining the adequacy of bridging are the ratio of the geometric mean antibody concentrations not less than .5, for noninferiority of the new pneumococcal conjugate vaccine relative to Prevnar, and less than a ten percentage point difference in proportions responding above the predefined antibody threshold barrier or titer.

Can I have the next slide?

It has also been proposed or it's conceivable to use single antibody concentration cutoffs for all vaccine serotypes, and one might choose for this purpose an antibody concentration at or above the highest threshold level observed for any of the serotypes to assure that more stringent criteria are met for all these serotypes.

And then, of course, the additional immunological parameters such as opsonophagocytic activity, measurement of antibody avidity, or a combination of the above that may perhaps be considered as predictors of efficacy, and the relevancy of these parameters in this context were discussed during the recent NIAID-FDA workshop and will be presented to you shortly.

I would like to note, however that

establishing of noninferiority based on sero-response rates, GMCs and/or additional immune parameters vis-a-vis the licensed product Prevnar could be a difficult standard to meet. With seven serotypes in various sets of endpoint criteria, the statistical analysis complicated by issues of multiplicity due to the various comparisons that would need to be made, as well as issues regarding a level of correlation of these different measures.

So the probability of failure to demonstrate noninferiority for one of the parameters will increase with each comparison that is made and could be due to chance alone.

And going back to antibody levels for a second, because Prevnar was highly efficacious in preventing invasive disease, the antibody levels attained following Prevnar may be in excess of levels required for protection from invasive disease. That is, other vaccine formulations might still be effective even if the antibody levels achieved are significantly lower than those achieved following immunization of subjects with Prevnar.

I'd like to briefly talk about the concept of performing clinical endpoint efficacy studies. Demonstration of preventive efficacy for clinical

endpoints remains the gold standard to support licensure of vaccines.

However, efficacy data based on clinical endpoints are likely to be difficult to obtain for future pneumococcal conjugate vaccines. As discussed, Prevnar was shown to be highly efficacious in a large trial for the primary endpoint of invasive disease, and as a result, Prevnar is currently recommended for universal immunization of infants in the United States, and this recommendation has been made by the American Academy of Pediatrics, American Academy of Family Physicians, and the Advisory Committee on Immunization Practices.

Now, if efficacy studies are required, then to obtain U.S. licensure for a new pneumococcal conjugate vaccine, such studies would need to be designed either as noninferiority studies using Prevnar as a comparator or superiority studies using placebo or an unrelated vaccine in the comparator group, depending on the availability of Prevnar in the host country.

In the latter case, if clinical efficacy was demonstrated for a new vaccine in either placebo controlled or non-pneumococcal vaccine controlled studies, one might still question whether the new

products were as effective as Prevnar, and thus the efficacy estimate was very high.

And some would argue that all pneumococcal vaccine studies should be conducted as comparative studies using Prevnar in the control group regardless of availability of Prevnar in the host country, and this is based on ethical concerns.

Clearly, the ethical evaluations and considerations of placebo controlled pneumococcal vaccine studies are very difficult and complex, and these are currently being discussed by FDA or between FDA upper management and the Office of Vaccines.

Next slide.

If efficacy trials conducted in foreign countries are to be used in support of U.S. licensure of new pneumococcal conjugate vaccines, immunological bridging to the U.S. population is likely required.

However, age specific disease incidence and population differences in genetics, nutritional status and background infection may affect the efficacy as well as the immune response induced by a particular vaccine.

So if efficacy is demonstrated in a non-U.S. population, demonstrating that the immune response is adequate in the U.S. population may be

difficult in the absence in a true correlate of protection.

Next slide.

Studies demonstrating noninferiority clinical endpoint efficacy for invasive disease would be substantially larger than placebo controlled trials, but in order to more fully evaluate the regulatory options on which to base licensure of new pneumococcal vaccines, the Division of Biostatistics within CBER has estimated sample sizes for efficacy trials using noninferiority trial designs.

And since future pneumococcal conjugate vaccines will likely contain more than the seven serotypes that are currently contained in Prevnar, it is plausible that fewer cases of all pneumococcal disease would be observed in the group receiving the higher valency vaccine than in the Prevnar group, but serotype specific efficacy in the Prevnar group may still be superior.

So, therefore, the more appropriate endpoint for comparative efficacy studies might be disease caused by any pneumococcal serotype, and of course, if studies are conducted in non-U.S. populations, differences in the epidemiology of pneumococcal disease may also affect the efficacy of

vaccine.

So in computing sample sizes for noninferiority efficacy studies for invasive disease due to all pneumococcal serotypes, the statisticians have made various assumptions of vaccine efficacy and pneumococcal disease rates, and these I will show in the next few tables.

But I would like to stress that the sample sizes reflect estimates rather than precise numbers, and the computed margins for the acceptable difference in vaccine efficacy between the new vaccine or the new product in Prevnar of ten, 15 and 20 percent that we show do not necessarily reflect CBER's thoughts on what would have constituted an acceptable difference.

Now, the first table that shows sample size estimates for invasive disease studies in the low incidence population evaluating noninferiority of new vaccines to Prevnar, and the assumption is made that the invasive disease case rate in the unvaccinated population is about 1.5 in 1,000, and what you can see here in the left column is the Prevnar vaccine efficacy estimate, the point estimate that we have specified to be between .7 and .9, and note that the efficacy for Prevnar in terms of protection against all pneumococcal disease was 90 percent in the Kaiser

trial.

The next column then here is the disease probability in the Prevnar group specified for these different point estimate of vaccine efficacy for Prevnar, and these three columns represent the case rates for the new vaccine group corresponding to a difference in efficacy between Prevnar and the new vaccine of ten, 15, and 20 percent.

So, for instance, if the true efficacy for Prevnar were to be .7, the disease probability in the new vaccine group could be no greater than six in 10,000 for this vaccine to be considered noninferior over the ten percent margin.

But the sample size required to show this would be 250,000 subjects per group. Now, if you assume a vaccine efficacy of .9, the sample size would drop to about 80,000 per group, but the disease probability in the new vaccine group could not be more than three in 10,000.

So what this table shows us is the numbers that would be required for such trials are very large, and that they increase as the Prevnar vaccine efficacy estimate decreases and as the acceptable margins between vaccine efficacy of Prevnar and new vaccine decreases.

And of course, the sample sizes are so large because the disease case rate in the unvaccinated population is so low.

Can you show -- okay. Thank you very much.

This slide shows basically the same thing, only here we have assumed that the invasive disease case rate in the unvaccinated population is about five instead of one in 1,000. And so now if you look at the Prevnar vaccine efficacy estimate of .9, you will need about 25,000 subjects per arm to demonstrate noninferiority of the new vaccine group within a ten percent margin.

Can I have the next slide, please.

Available efficacy estimates for Prevnar in preventing otitis media due to serotype specific pneumococcal disease are substantially lower than for invasive disease, and the level of preventive efficacy that is supportive of an otitis media indication is currently under review by the FDA.

If the level of efficacy reported in the Finnish efficacy study is deemed sufficient to support an otitis media indication, an indication for prevention of otitis media based on noninferiority to Prevnar could be requested by manufacturers without

prior demonstration of protection against invasive disease.

And efficacy studies based on otitis media endpoints would likely be conducted in countries like Finland where tempanocentesis as therapy for acute otitis media is standard of care.

So in planning noninferiority trials for the efficacy endpoints for otitis media due to all pneumococcal serotypes, our biostatisticians have made assumptions based on data from the Finnish otitis media trial of Prevnar in calculating sample sizes, and this is shown in the next table.

Next table.

And here we assumed, and these are the data from the Finnish trial, that the true vaccine efficacy point estimate for prevention of cases due to all pneumococcal serotypes is 34 percent, and that was the efficacy for Prevnar.

The left column then shows -- this table is set up a little different -- this column shows the acute otitis media case rate in the unvaccinated population per person-year, and this is then the case rate in the prevnar group assuming that the vaccine efficacy is 34 percent.

And, for example, using a case rate in the

unvaccinated population of .4 and a vaccine efficacy for the new vaccine of 30 percent, you would need about 6,000 subjects per group to demonstrate noninferiority of the new vaccine, and the sample sizes do drastically increase as the case rate in the unvaccinated population decreases and as the acceptable or the vaccine efficacy of the new vaccine compared to Prevnar narrows.

Now, recommending bodies, such as the American Academy of Pediatrics or the ACIP, may not be completely assured that vaccines that are licensed based on prevention for otitis media will be as effective as Prevnar in preventing invasive disease. However, neither does demonstration of noninferiority of immune parameters provide this assurance in the absence of a quantitative immune -- for invasive disease.

And I would like to conclude here and present you with the following items for discussions for this afternoon.

First, please discuss whether noninferiority immune response trials comparing new pneumococcal conjugate vaccines with Prevnar are sufficient for inferring efficacy against invasive disease for the new product, and if so, what

immunological parameters should be considered?

Next slide, please.

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

And next slide, please.

Please discuss the following scenario. An invasive disease efficacy study may be performed in a non-U.S. population with a new pneumococcal conjugate vaccine. If efficacy is demonstrated could data derived from such a trial support licensure of the vaccine in the United States?

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

And the next slide.

Please discuss if efficacy studies -- if invasive disease efficacy studies cannot be done, please discuss if data demonstrating clinical efficacy against acute otitis media for a new pneumococcal conjugate vaccine can also be used to infer efficacy against invasive pneumococcal disease for this new product.

Next slide.

And in the last slide now I would

acknowledge the contributions and invaluable help that I received from my colleagues in putting the briefing document and the slides together, and especially Dr. Douglas Pratt and Pamela Getson and Peter Lachenbruch, who were our biostatisticians.

Thank you.

ACTING CHAIRMAN DAUM: Thank you very much, Dr. Gruber.

I would like to ask the committee at this point whether they have questions specifically to clarify items in Dr. Gruber's presentation. We will obviously be addressing the bigger issues beginning after Drs. Frasch and Falk present the synopsis of the workshop.

Dr. Kim.

DR. KIM: In immunologic parameters, you talked about single antibody concentration curve and opsonophagocytic assays, and antibody avidity assays, and you gave us a sort of a graph utilizing serotype 6B and to discriminate vaccinated versus unvaccinated.

Are you able to make such discrimination curve using other parameters besides antibody concentrations, such as opsonophagocytic assay and so on?

DR. GRUBER: I am actually not sure about

this at this time. I don't really know if the data are available. Perhaps this is a question that we could ask the manufacturers who are looking at these assays more closely than we have seen these assays.

ACTING CHAIRMAN DAUM: Other clarity questions for Dr. Gruber?

Dr. Giebink, Dr. Broome next.

DR. GIEBINK: Dr. Gruber, along the same lines, I wonder if in the licensure of the 14 and 23-valent polysaccharide vaccines was this approach of antibody difference between immunized and nonimmunized subjects ever used or discussed?

DR. GRUBER: No, it was not used as far as I know. That has not been used, and I doubt that it was discussed. People that have the history at CBER could perhaps comment on this.

Dr. Frasch, would you like to make a comment?

DR. FRASCH: Yes, I happened to be here during the approval.

No, the only thing that they had to demonstrate was that they had a comparable fourfold increase in antibodies -- remember we're talking about adults now -- in antibodies to the types not included in the 14-valent vaccine, and show that each of the

new types induce functional activity, i.e., opsonophagocytic activity.

There was no discussion about thresholds.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Broome, please.

DR. BROOME: Marion, I'm curious in your sample size calculation. Your background rate appears to be invasive pneumococcal disease, but of course, the efficacy of 97 percent is against vaccine type pneumococcal disease.

So when you look at the vaccine efficacy estimate, I assume you need to factor in the proportion of types covered by the vaccine, i.e., you have to compare a disease rate that's for the same spread of serotypes as the efficacy rate.

DR. GRUBER: Yeah, that point is acknowledged. I think what we've done really purposely is we've said that we wanted to consider really invasive disease against all pneumococcal serotypes, and so, therefore, in computing the sample size calculations we have actually looked at perhaps vaccine efficacy estimate for Prevnar than it was actually demonstrated.

But it's clearly true that disease epidemiology and other preventive serotypes then need

to be factored in if you want to make precise sample size estimates for such trials in a specific setting.

ACTING CHAIRMAN DAUM: I would think the same argument would be extended to the otitis media issue as well.

DR. GRUBER: That's right. And this was only to give you really sort of a ball park figure, you know.

DR. BROOME: But, yeah, I think what we're saying is the realistic overall efficacy of Prevnar would be more like --

DR. GRUBER: Well, more like perhaps 90 percent, but then, again, you know, if you look at a Third World -- I don't want to say that. I don't want to --

ACTING CHAIRMAN DAUM: Developing country.

DR. GRUBER: Right. In developing countries, there may be other pneumococci serotypes, pneumococcal serotypes prevalent, and so the vaccine efficacy for Prevnar may even drop because perhaps other serotypes would be responsible for invasive disease.

ACTING CHAIRMAN DAUM: Ms. Fisher, please.

MS. FISHER: As natural exposure to pneumococcal organisms is widespread in the U.S. in

most populations around the world, will the presence of maternal antibodies or preexisting antibodies from natural disease exposure to any of the vaccine serotypes affect the qualitative and quantitative measurement of post vaccination functional antibodies?

In other words, could the vaccine's efficacy using serologic immunologic markers be over or underestimated because of the potential confusion between vaccine and disease induced antibodies?

DR. GRUBER: Well, I think you have to -- I mean, I'm hearing you actually saying two issues. One is the material antibody issue, and the other one is disease induced antibodies. I think these are two different things.

In terms of maternal antibodies, since we're looking at -- if we were to look at antibody threshold levels, we would be looking at seven months of age basically where you have completed giving a primary series of vaccine, and at that point, from the data from what we've seen is that the antibody levels really have dropped by six, seven months of age.

So I, and other people may comment on this as well, I would not necessarily expect maternal antibodies to be really a significant confounder there.

In terms of antibodies due to vaccine, to -- induced by disease, it's difficult. I'm really -- I mean, I don't really see right now how we can really apply this here because if you have an infant that has invasive disease, like at three, four, five months of age, you probably would not really --

MS. FISHER: It doesn't have to be invasive disease, does it?

DR. GRUBER: No, it doesn't have to be invasive disease.

MS. FISHER: Simple exposure to the --

DR. GRUBER: That's right. It can be exposure. Well, I guess that's a potential.

MS. FISHER: I think it's an important potential.

DR. GRUBER: Well, I think we may have to factor this in or comment on this in this afternoon when the committee discusses this issue.

ACTING CHAIRMAN DAUM: I think we could return to that issue later should you so wish it, but we're looking for questions to clarify Dr. Gruber's presentation right now.

DR. KOHL: I think you alluded to a ten percent difference in terms of acceptability for noninferiority, and yesterday we heard a plea by one

of our statisticians that the FDA join the rest of the world and use a five percent difference. Is there any validity in that or any thoughts on FDA's part about what kind of difference?

DR. GRUBER: You know, I do not, yeah, really think that a decision in this regard has been made. The data that I showed was really that we have previously induced in the bridging study that was done for Prevnar. So I think we need to have perhaps further discussions on this issue.

But Dr. Lachenbruch would like to make a comment.

DR. LACHENBRUCH: Peter Lachenbruch, FDA. I'm one of the statisticians.

I believe -- I wasn't here yesterday, but I believe the issue was the confidence level should be 95 percent as opposed to 90 percent, not the lower bound of the interval on vaccine efficacy, and that's a little bit different, a lot different.

ACTING CHAIRMAN DAUM: Thank you for clarifying that.

I think at this point we'll thank Dr. Gruber very much and ask Drs. Frasch and Falk to present a summary of the pneumococcal conjugate vaccine workshop.

As they get set up to present, I guess I'd like to compliment them in being able to get the synopsis together in near record time, as fast as it took to fly from Washington to Chicago and back it seems.

We're going to have both their presentations, and then, again, I would ask committee to offer clarifying questions specifically for the issues raised in their presentation.

DR. FRASCH: Okay. You've already heard some mention of the correlates of immunity workshop we held, that was held on February 26th. This was a joint workshop organized between the NIAID and CBER.

But first, I would like to give you a little bit of the history how this workshop came about.

Next. Okay. We just passed one.

All right. This whole thing got started shortly after the hemophilus conjugate vaccines were being developed. In 1986, NIAID, WHO, with WHO support, had a workshop on the NIH campus in which they looked at the need for a pediatric pneumococcal conjugate vaccine, and this workshop was where they actually had some of the experts of the world set up on the blackboard and select what they thought were

the seven most prevalent types.

And as it happens, those are the types that are in the licensed vaccine.

Next slide, please.

Then in 1987, NIAID put out an RFP for production of a clinical lot of seven-valent pneumococcal conjugate vaccine.

Next slide.

Then in 1988, Praxis Biologics was awarded that contract, and ultimately was able to provide a five-valent vaccine, and you will see a number of publications relating to a five-valent pneumococcal conjugate vaccine, and this all came from the studies sponsored by NIAID.

And then finally -- next slide -- in 1994, NIAID held a workshop on the potential uses of a pneumococcal conjugate vaccine, and one of the potentials they saw was for infants, also adults, but also pointing out that the need of a pneumococcal conjugate vaccine may even be greater in other countries than just in the U.S.

So with that background -- next slide -- I want to give sort of the rationale why we held the workshop a couple of weeks ago.

First, as you heard today, there are going

to be immunological comparisons between conjugate vaccines, and therefore, we need to have a scientifically sound basis for considering new conjugate vaccines and clinical evaluation of future pneumococcal conjugate vaccines will certainly include studies of antibody response.

Next.

Thus, the purpose of the workshop was to discuss our current understanding of the mechanisms of immune protection against invasive pneumococcal disease, and then to identify those in vitro immune measures which can serve well as correlates of immunity in future vaccine trials.

Now, next slide.

I would like to momentarily take you back a few years and look at the historical perspective gain from the Hib vaccine experience, and I'm sure you're going to hear about hemophilus conjugates against today because the hemophilus conjugate was the first licensed conjugate vaccine.

So what we see is that in October and December of 1990, the first two hemophilus conjugate vaccines were licensed. These both were licensed on the basis of randomized controlled efficacy trials conducted at the same time.

Next slide.

Pasteur Merieux, now Aventis Pasteur conjugate vaccine was actually approved in 1993 over two years after the other two conjugates. Thus, what was the mechanism that the Aventis Pasteur vaccine became licensed, U.S.? I'll go through those.

First, they were randomized comparative immunogenicity in infants with a similar currently approved product.

Two, the persistence of antibody after the primary immunization series and up to the time of the recommended booster dose was looked at.

Third, they were able to show as all conjugate vaccines should that the infants were primed by the conjugates for a subsequent booster response to the native hemophilus polysaccharide given six to nine months after the primary immunization.

Why was this important? Because this would simulate natural exposure and demonstrate immunologic memory. The importance here is that antibody levels at seven months is what is critical for protection, but in an older individual, memory also becomes quite important.

So next slide.

So the last point was they had to show

functional capacity of the conjugate induced antibodies by either measuring opsonic or bactericidal activity. Well, bactericidal activity was okay for hemophilus. For the pneumococcus, one would have to concentrate on opsonic activity.

So the focus on the workshop was invasive disease. Why was that focus? The focus is because -- I'm quoting now from the Prevnar package insert -- "Prevnar is indicated for active immunization of infants and toddlers against invasive disease caused by pneumococcal types included in the vaccine, and these types are 4, 6B, 9B, 14, 18C, 19F, and 23F, and the routine schedule is a four-dose schedule at two, four, six, and then 12 to 15 months of age."

So next slide.

Here are some important items that were discussed during the workshop which will be greatly expanded upon very quickly by Dr. Falk.

First, the mechanism of protective immunity was discussed.

Second, the measures of immunity that correlate best with protection.

Next, the immunological parameters that would need to be evaluated in a head-to-head comparison of a pneumococcal conjugate vaccine with a

currently licensed product.

And finally, how to evaluate the immune response to serotypes not contained in seven-valent vaccine. As you know, the newer vaccines will have higher valency. So what to do about those types not in the current vaccine.

Thank you.

DR. FALK: Well, I want to thank Dr. Frasch for inviting me to share with you some of the highlights of the CBER-NIAID workshop that really specifically dealt with addressing some of the issues of the correlates of immunity as we understand them currently.

And as was mentioned, this workshop occurred just about a week ago, and so what I will be presenting to you is really an attempt to just abstract some of the main items and conclusions that were generated from that workshop.

And also, as I go through the talk, I'm going to focus on the particular presentations that we had and some of the highlights, following by a summary of what the expert panel and discussees had come up with, some conclusions, and also at the very end, which I'm sure everybody is going to be happy to see, are a list of unresolved issues, and I think that that

will certainly play into -- no comment on how long that is relative to the rest of the talk -- that will certainly play into your discussions this afternoon.

Now, if I could just have the next slide, please. Next slide.

I'm here today. What we see here is the workshop objectives, and I'm here today on behalf of NIAID serving as a rapporteur for this workshop, and so that was the role that I played, along with Mark Steinhoff was a co-rapporteur.

Well, we can see here the objectives of the workshop were really showing a partnership between NIAID and CBER in an attempt to come to grips with a very difficult question that is necessary to deal with in order to advance the public health interest in regarding pneumococcal vaccines and also combination vaccines which include pneumococcal antigens.

So what we were dealing with here is a mechanism that we were hoping to move forward that would advance the clinical development of these conjugate vaccines for their use in children, and the main objective was to identify and discuss the immune measures as correlates that we could be taking for clinical studies, which Marion Gruber had highlighted early in her talk, and also hopefully to develop a

framework for evaluation of pneumococcal conjugate vaccines for their use in children.

If I could have the next slide.

Just to give you a sense of the make-up of this workshop, there were certainly a panel of experts that had been invited to serve as the main input for the workshop, and a number of those experts had given very brief presentations on a number of specific topics which you'll see later.

We had industry representatives there as well. We had NIAID staff, and CBER staff.

With regard to the experts, you'll see them mentioned specifically for those who had given presentations, but I also wanted to highlight some additional persons who were there.

Dr. Donna Ambrosino; we have Steve Black, you'll see; George Carlone from CDC. Bob Daum had participated. Ron Dagan; Kathy Edwards; David Goldblatt. We had Helena Kayhty, Daniel Musher, Lawrence Moulton, Moon Nahm, Mark Steinhoff, Benjamin Swartz, and Mathuram Santocham, Jeffrey Weiser, just to give you a general overview of who was at the table for these discussions.

It was a very interactive session that allowed participants who were not at the table to also

interact.

If I could have the next slide, please.

The presentations were specifically asked to focus on mechanisms of protection for pneumococcal conjugates and pneumococcal disease, correlates of protection, antibody quantitation focusing on ELISA and opsonophagocytic assays. Also a comparative response from different vaccines was also included in this.

Issues of immunologic memory, and the challenges of choosing endpoints for clinical studies based on comparisons to Prevnar.

Next slide.

This is the beginning of an introduction to you with just abstracting some of the main bullets from each of the individual invited talks that we had had. The first one shown here was by Dr. Musher on the mechanisms of protection against bacterial pneumococcal disease.

And what you can see here is that he basically talked to us about what was shown with passive transfer of polysaccharide antibodies in rabbits and how that was used to identify serotype specific protection.

He also discussed age related differences

in protection following polysaccharide vaccine. This is straight polysaccharide. This is not conjugate. And also he highlighted that nonfunctioning antibodies, i.e., non-opsonophagocytic or protective antibodies, may be elicited following infection. So it sets the stage for how complex the immune response can be.

Okay. Next slide, please.

Our next speaker was Dr. Santosham, and what he was asked to talk about here was what was known about correlates of protection, and this was really lessons learned from passive transfer, and what we have here is he described to us some of the information that was obtained for hemophilus polysaccharide induced antibodies that were shown to demonstrate passive protection.

He also had immunologic findings based on the polysaccharide, but also clearly indicated that it may not -- that what we know obtained from data obtained from polysaccharide vaccination may not be relevant actually for consideration for conjugates.

He also described for us some information that was obtained using a bacterial polysaccharide immunoglobulin passive transfer for what we know about protection. The BPIG is a complex antibody mixture

and was used to look at Hib, Haemophilus influenza short-term protection and pneumococcal -- and conjugate following -- I'm sorry. That should be pneumococcal protection following the bacterial polysaccharide immunoglobulin. That's a typographical error.

If I could have the next slide.

His conclusions were that breakthrough cases suggest that antibody titer may not always been protective. Passive immunization also suggests that there are similar thresholds for pneumo and Hib polysaccharides induced, and this is short-term protection.

Next slide, please.

The next talk we had was really a synopsis presented to us by Dr. Black which is information that was obtained from the Prevnar efficacy study, sine he was one of the principal investigators from that study.

And what he discussed for us and presented for us was type specific protection and also what we might have gained about knowledge about correlates of protection from the Kaiser efficacy study for Prevnar.

As summarized here is just a brief overview of what the information was surrounding that

trial. It was a double blind, randomized, controlled trial in approximately 38,000 infants. The efficacy results, you'll see various numbers for efficacy, and it really depends on when the efficacy analysis was calculated based on follow-up time, but the results he presented were that there was 97 percent efficacy from base of disease; 87 percent for pneumonia; eight percent for otitis media visits; and approximately 25 percent for ear tube replacement.

If I could have the next slide.

What he also presented to us was some breakdown on what information was available on type specific protection, and what we see here is serotype specific efficacy, was approximately 100 percent for types 14, 18C, and 23F, and 85 percent for 19F, and it also needs to be noted that there were instances where there were no cases for certain serotypes in the vaccine. So a protective efficacy could not be determined in those cases.

Next slide.

Dr. Black also presented some of the immunogenicity data post dose three that was derived from a subset of children in the efficacy study, and basically what he tried to do was to focus on looking at two antibody threshold levels and looking at the

percentage of responders that were observed in the efficacy study.

The first threshold that he evaluated was the percentage of subjects with greater than 0.15 micrograms per mL of anti-pneumococcal antibody, and what was shown here is that 100 percent of the subjects that were evaluated for immunogenicity showed a response greater than .15 for all of the serotypes except for 23F.

If you then looked at a cutoff value, a threshold value of 0.5 micrograms per mL, you see a slightly different pattern, and there 87 to 90 percent of the children achieved that level of 0.15 for all the serotypes except for serotype 6B, where only 72 percent achieved a 0.5 microgram per mL level.

He also noted that from the study there appeared to be a GMC range from 1.4 to five micrograms per mL for various vaccine serotypes, and the take home message from this was that the protective levels may differ by serotype and by disease, and when I say disease, I mean might differ for invasive disease versus pneumococcal pneumonia, versus otitis media.

If I could have the next slide.

We then had the opportunity to hear from Dr. Kayhty from Finland, where she presented data on

studies on the immune response to different pneumococcal conjugate vaccines as evaluated in Finnish infants.

I view this as a rather important part of our discussion because here it was an evaluation of different types of vaccines, and the different types of vaccines may be impacted by the fact that they might be on very different carriers, and also, they also may have very different conjugation processes, and so this was actually looking at the ability to look across vaccines to look at their immune responses.

And some of the summaries from that particular talk were that the immune response to different pneumococcal conjugates could be compared across studies, and the response to serotypes may differ from vaccine to vaccine, but they should actually have an opportunity to look at a number of different populations, as well, from different countries and what was noted, that the populations can show differences in immune responses even to the same vaccine.

And also, she had provided some information about a comparison of kinetics across vaccines and how that might actually help in

understanding some of the mechanisms of immunity.

Next slide, please.

We also wanted to have a discussion of the group regarding the particular assays that are available right now for evaluating pneumococcal responses, and Dr. Nahm presented us with some data and some information about antibody quantitation by ELISA as it compares to opsonophagocytic activity, and you'll see later that one of the conclusions from some of the early animal studies is that opsonophagocytic activity is a very good predictor and correlated with protection, and so that was the reason why we wanted to bring in what is known about the ELISA, which is what most of the particular comparisons that you've heard about today would be focusing on.

Dr. Nahm had highlighted that the opsonophagocytic assay is actually very difficult to standardize. Optimizing of the ELISA assay was moving forward, and a lot of discussion was focusing on the fact that there may be a need to absorb sera to get rid of cross-reacting antibodies and substances; and that this cross-reactive antibody issue may actually be more relevant in adults and higher in adults than in infants; and also that depending on a number of different serotypes, that the correlation between

opsonophagocytic activity and the ELISA titer actually can vary depending on the particular serotype that's being evaluated.

And it was also shown that antibodies with higher avidity are more likely to correlate with the opsonophagocytic activity.

And if I could have the next slide.

The presentation by Dr. Goldblatt was to address the issue of what we know about immunologic memory and what are the various mechanisms for evaluating immunological memory or on the other flip side of that is also just demonstrate priming followed by conjugate vaccine administration.

Dr. Goldblatt for us summarized a number of the features of memory shown here, is that basically you can demonstrate memory by showing that a previous nonresponder now becomes a responder.

Memory has a rapid response, which means the kinetic of response is very quick. It's dominated by IgG1 antibody subclass, and that in the induction of memory you have an increased affinity avidity over time, and what was pointed out is that it appears that with conjugate vaccines, and pneumococcal conjugate, in particular, the avidity appears to increase over the course of the primary series.

Normally when people are discussing the issue of priming versus memory, it's in the context of administering a conjugate vaccine in the primary series, and the you follow by a polysaccharide only boost, and then show that you can get an enhanced response, a quicker response or people who were nonresponders are now responders.

What was shown here, and personally was very interesting, was that with the conjugate vaccines you actually see some of the hallmarks of memory showing up even over the course of the primary series.

And if I can have the next slide.

Dr. Dagan was tasked with, I think, a very difficult presentation, and attempting to summarize for us and raise to the table the dilemma of choosing endpoints for future comparative studies. One of the things he had pointed out was that for study design it's most -- you know, most envision that it would be a double blind comparative study to Prevnar.

It was also proposed from Dr. Dagan that this is going to be a difficult question and that you're actually going to have a constellation of immunogenicity endpoints to be evaluated, present responders for short and long-term protection, as an example, an evaluation of geometric mean

concentration, also an evaluation of functional activity, as well as the concept of avidity maturation and memory.

Next slide, please.

With regard to some of the additional components of studying a vaccine for licensure, comparing it to Prevnar, we cannot overlook the fact that safety would also be an important part of that characterization and requirement for licensure.

He also raised the possibility that an evaluation of the pneumococcal conjugate vaccine effects on carriage might also be important information to highlight that may be able to be factored into the comparative analysis.

And it was felt that the demonstration, the bar would be set for noninferiority to Prevnar, and also attempts would be made to try and see if there were new correlates for the new serotypes. What would we be using for those new serotypes because they obviously were not going to -- we can't draw on the Prevnar experience in that case.

Next slide.

Dr. Dagan raised the very difficult question here of what would be the proposals for how would you evaluate these multiple endpoints, and one

provocative I'll say proposal that he put before us was that you would actually be looking at an accumulation of the total score across all of the new serotypes plus the Prevnar serotypes.

He also discussed possibility of weighting responses for the various serotypes based on a number of different parameters. Shown here is the possibility of having a weighted average based on serotypes that might be associated with antibiotic resistance.

Also, should we be weighting the average to be based more on its comparisons to the common serotypes with Prevnar, and how do we weight the impact of the new serotypes that are not in Prevnar?

Next slide, please.

As you can see here, a common theme was focusing on obviously the immunological quantitation of the antibody response, and we were very fortunate to have Dr. Kohlberger provide us with one possibility statistical approach to establishing this threshold.

It was clear, as Dr. Gruber had pointed out, that the fact that Prevnar has such a high efficacy rate created a bit of a problem for trying to establish a correlate of protection, and so what we were ending up with is a discussion really of how to

establish a threshold of comparison.

And I'm happy that Dr. Kohlberger is in the audience. So if he has any comments on the slides, he would be the most appropriate person to direct that to.

But here was kind of taking some lead on the fact that thresholds had been established for Prevnar for a very different purpose, as Marion Gruber had mentioned earlier. Here we were going to basically be looking at an ability to try and set a threshold that would hopefully be relevant to the level of efficacy seen with Prevnar.

And show here is population probability of disease. These are just some of the bullet points form the talk. The population of the probability of disease was relative to the proportion of subjects with an antibody concentration less than the threshold. So as you are below this threshold, your probability of having disease would increase.

And that was the premise, and so how did we get to setting this threshold? One proposal was based on the only efficacy data we have, was based on the Kaiser efficacy study, and it was looking at the reverse cumulative distribution curves for the various populations of the Prevnar group and also we also in

that particular study, we had a meningococcal control group.

When we looked at the responses to Prevnar, Dr. Kohlberger had indicated that if you look at the aggregate of the responses for all of the serotypes, it appeared that there was greater than .18 micrograms per mL correlated with vaccine efficacy, meaning that as you looked across the reverse cumulative distribution curve, as you got close to the .18 microgram per mL range, you had close to 100 percent of your subjects responding, which is relative to the efficacy seen in Prevnar.

One of the assumptions is that, in this model, is that there's no difference in serotype specific efficacy.

Could I have the next slide, please?

And this basic model assumes that all subjects were exposed, but that true exposure rates cancel in vaccine efficacy calculations, and it also assumes that all populations are alike for efficacy and immune response.

And one thing that did have to come out from this talk is that there is an impact of assay standardization and also comparability between assays to be able to begin setting your threshold. Of

course, these special values that we talked about were really from the Wyeth Lederle laboratories, and so another manufacturer's laboratory has an assay that behaves slightly differently. It's very hard to just take an absolute threshold value from that.

The next slide I'd just like to share with you what the panel was actually -- the specific questions they were asked to discuss, and the first question was a variety of animal models point toward the pivotal role of anti-polysaccharide antibodies and the protection against invasive pneumococcal disease.

What is known of the functional basis for protection?

Next.

Based on what is known about the mechanisms of antibody mediated protection, what are the characteristics of the antibody response most associated with protection?

Next.

What <u>in vitro</u> assays are most relevant to measure for these particular immune parameters? If new pneumococcal vaccine conjugates are compared to a licensed conjugate, what critical immunological parameters should be evaluated in the clinical studies?

Next slide.

Based upon our present understanding of protection, are the currently available immunological assays adequate to assess parameters that form the basis for immunological bridging to clinical efficacy?

Next.

How should the immune response to serotypes not included in the licensed vaccine be evaluated? What is the importance of functional assays in this evaluation?

And also we invited the panel to discuss any other issues.

Now I'd like to get to the summary. I'm not going to address each of these questions specifically. I'm just going to give you an encapsulated version of what the responses were to these questions.

The panel felt that the animal data certainly supported the role for functional antibody production as the basis of protection. The caveats though: functional antibodies may be difficult to standardize. Standardization efforts are more advanced for the ELISA method.

The next point was that antibody avidity may contribute to protection. Also, antibody

concentration is important for short-term protection and memory for long-term protection.

Next slide.

The GMCs and percent responders are important parameters. We should focus on threshold level, not a protective level because it was felt that a protective level could not be identified from the Kaiser study.

Direct comparison of vaccines head to head is important to help control for assay variability, and there's also a caution against relying too heavily on our Hib experience, and cited here is the fact that we really need to look at pneumococcal conjugates in and of themselves and partially due to the fact that the disease and organism profiles are different for pneumococcal than Hib.

The conclusions that the panel had come up with were that ELISA antibody levels are meaningful. A protective level may not be identified from the efficacy study or was not identified. Avidity and functional antibodies may also be important.

Highlighted here was that this importance might be weighed perhaps a little differently for new vaccine serotypes, and that it was noted that this particular comparison of the functional antibodies to

ELISA may be appropriate to evaluate in a subset either prior to the pivotal study or during the Phase 3 study, and that one of the limitations of measuring avidity and functional antibodies is due to the difficulty in standardizing these assays.

Next please.

Following much discussion, it appeared that the -- well, the group felt most strongly that the primary endpoint should be the percentage of responders achieving a predefined threshold.

They noted, however, that multiple endpoints should also be evaluated.

Reverse cumulative distribution curves are also important measures of comparing the different population responses in the comparison.

It was also noted that antibody responses post dose three and post dose four are important. Post dose three antibody responses should be considered as primary endpoints partially because that might be the most critical comparison and most sensitive comparison with regard to the quantitation of antibody.

It was also noted that the kinetics of the response are also important in this comparison, and also a demonstration of memory was a component that

they felt was necessary for the pneumococcal conjugate vaccine comparisons.

And for new serotypes in particular, the issue of priming versus memory and memory are very important and should be considered as part of the evaluation.

The next slide gets to the unresolved issues. Although they agreed that memory was an important component of the antibody profile, how do you test for memory if Prevnar is a four-dose series? What is an appropriate control group? Will it be necessary to compare the historical controls? Should memory also be evaluated for serotypes where field efficacy was not established?

Should avidity maturation and carriage also be evaluated?

Next slide.

With regard to the establishment of a threshold value, should a single threshold value be assigned or should the criteria be serotype specific? Should the aggregate response from the Kaiser efficacy study establish the single threshold? Should a single more conservative threshold be used? Could the lowest RCDC curve from the efficacy study be used as a minimum threshold?

Next.

This one our statisticians will probably appreciate. What will the impact of noninferiority criteria -- will what be the impact of noninferiority criteria, given the number of antigens and endpoints to be evaluated?

Should the importance of serotypes be weighed for Prevnar versus non-Prevnar serotypes? How do you consider those serotypes for which field efficacy was not demonstrated? How do you weigh the importance of serotype response based on disease prevalence?

Next slide.

What will be the impact of noninferiority criteria? The same question, but now the last point: how do you weigh the importance of serotypes associated with antimicrobial resistance?

I hope that this summary will help you in your discussions this afternoon with regard to the experts' evaluation of what is and is not known with regard to evaluating pneumococcal conjugate vaccine responses.

Thank you.

ACTING CHAIRMAN DAUM: No, thank you. That was an absolute "tour de force."

(Laughter.)

ACTING CHAIRMAN DAUM: And I'm sure the committee is very grateful for all that information.

What I'd like to do now is to have some committee discussion questions regarding Drs. Frasch's and Falk's presentation for clarity purposes, and then we'll have open public hearing. We'll go to lunch, and then we'll come back and deal with the easy questions that we've been posed by our FDA colleagues.

I'm going to start with Dr. Kohl, Dr. Hall, then Dr. Wharton.

DR. KOHL: Dr. Falk, thank you, and can I ask you to elaborate on some of the points of Dr. Kayhty's presentation? In particular, tell us a little bit about different immune responses in populations with the same vaccine.

DR. FALK: Sure.

DR. KOHL: And how that's pertinent to this country, as well.

DR. FALK: Okay. What I'm going to do is I'm going to start with a caveat. This meeting happened one week ago, and I am going to be very couched in the specifics in fairness to the presenters until we've had time to actually go over the slides and present them in the correct format, but I will

give you a very general synopsis though.

What was found in her evaluation, she had looked at similar vaccines assayed or evaluated in a number of different countries, such as Finland, the Philippines, and Israel. What she found when she looked at the immune responses was that there were different levels of antibody responses in the various populations, and the Philippines seem to have been pretty much an outlier so to speak because the responses were much higher to the vaccine.

And so I think the pertinence of that is to say that when you are evaluating responses, you have to understand that depending on the population you're evaluating them in, they may or may not be readily translatable to, for instance, a U.S. licensure, and that could present a problem.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Hall is next. Then Dr. Wharton, Kim, and Goldberg.

DR. HALL: Thank you.

I'm wondering if you have more information about the associations with antibiotic resistance in the serotypes, both in the vaccine currently and what would be proposed.

In particular, is there a correlation with those serotypes which are more frequent or with particular clinical disease or with immunogenicity? In other words, also what would be the effect, I'm trying to get at, of the vaccine on antibiotic resistance in those serotypes, particularly those that are not included in the vaccine or those for which there was no efficacy shown?

DR. FALK: This particular workshop really presented no data as to the antibiotic resistance profile for the serotypes or the impact of vaccination on the generation of resistance. So that was not actually discussed in any detail at the workshop.

It was just raised as a possible public health issue that may or may not play into discussions of how you evaluate the importance of meeting noninferiority criteria for a number of different serotypes.

But I don't know if Dr. Frasch wants to comment any more outside of the workshop.

DR. FRASCH: I would only say that as it turns out, all of the really important antibiotic resistant strains, serotypes are included in the present seven-valent vaccine, and that it's really not an issue if we talk about greater multi-valency versus

that.

ACTING CHAIRMAN DAUM: Okay. As we move on, I'd like to remind committee members that we're asking for clarification for the presentations we have here. We will have time to return to antibiotic resistance and vaccine serotypes if you so wish this afternoon.

I have Drs. Wharton, Kim, Goldberg, Faggett, and Broome.

Dr. Wharton, please.

DR. WHARTON: I just wanted to clarify what was in the presentation from Dr. Santosham about the lessons learned from the bacterial polysaccharide immune globulin. I understood that there was a correction of what was on the slide, and it wasn't clear to me if the lessons were about Hib or pneumococcal disease or both.

DR. FALK: His discussion focused on the ability of measure the efficacy for Hib and pneumococcal disease following BPIG administration, and what he had shown is that there appeared to be some degree of similarity with regard to the threshold that was needed to demonstrate short-term protection because, of course, this was given like every three months.

ACTING CHAIRMAN DAUM: Dr. Kim, please. Oh, sorry.

DR. FRASCH: I should point out that only the Hib data has actually been published.

ACTING CHAIRMAN DAUM: Dr. Kim.

DR. KIM: Sine this workshop was with experts, I'm just curious to know whether there was any discussion about immunologic responses to a particular serotype, for example, why 19F is a poor immunogen compared to other serotypes.

DR. FALK: They did not really delve into the specifics other than trying to acknowledge that there might be something related to the particular organism that might be involved in eliciting lower responses, but it was not really talked about in detail.

DR. KIM: And the second issue is that since, as you indicated, immunologic assays may not be standardized, I wonder why there was, you know, emphasis on some in vivo models for looking into the protection, such as animal model, which you briefly indicated in your earlier slide.

DR. FALK: I'm not sure I understand the question.

DR. KIM: The question is that, again, you

say the opsonic assays and the antibody avidity assays, all of these assays, based on, again, your presentation appeared too difficult to standardize. So the question comes up is why not add some more traditional assays to look at the function of antibodies, such as animal protection studies, which you indicated in your earlier slide.

DR. FALK: Right, right. The sequence of events there was to actually lead you into -- lead into the understanding that antibodies (a) are important, and that was from the early work with the animals.

I think that the animal studies are also difficult to try and standardize and also perhaps are not as amenable to the quantitative comparisons that we would be looking for when we're trying to do the evaluation.

And so we stepped from introduction of the work we knew and the information we knew from the animal models to the fact that it appeared that the function -- a functional antibody was the important parameter, and then we had to bridge to how do we incorporate that information into our considerations for licensure.

Dr. Frasch, did you want to add anything?

ACTING CHAIRMAN DAUM: Thank you.

Drs. Goldberg, Faggett, Broome and Insel.

Dr. Goldberg, please.

DR. GOLDBERG: On the discussion of choosing endpoints for clinical for the comparative studies, there stuff in here about multiple endpoints, and you're talking about immunogenicity and other parameters. Was there any consideration given to discussion of combination endpoints, what I would call combination endpoints?

You know, the first occurrence of one of the illnesses that this vaccine could theoretically prevent, and in combination, you know, was any of that discussed? We can discuss it later as alternate ways of developing clinical trial designs.

DR. FALK: Well, this particular discussion focused really on the immunological parameters. So I think you might want to take that back up in the afternoon for possibly expanding that.

And Dr. Lachenbruch is, I think, wanting to respond.

DR. LACHENBRUCH: Dr. Moulton proposed a weighted sum of scores, and that turned out to be somewhat similar to things that we had been considering in the Division of Biostatistics.

DR. FALK: But, Tony, that's still related to immunogenicity.

DR. LACHENBRUCH: Yes.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Faggett, please.

DR. FAGGETT: Yeah. I realize this meeting was designed to look at in vitro immune measures that represent correlate's immunity for use in future in clinical trials. However, Dr. Dagan apparently in discussing the dilemma of choosing endpoints looked at studies for licensure to include safety in carriage.

What was talked about there?

DR. FALK: With regard to the safety, it was just the acknowledgment that whatever type of comparative study you propose would have to have safety as a component as well, period.

Carriage was another issue where in the absence of what was accepted to be a true correlate established for the antibody titer, that perhaps we could gather additional types of more clinical endpoints in the conduct of the study, and that was just a proposal that he had put forth, that that might be something that might weigh into the equation.

DR. FAGGETT: So safety would be discussed

in another forum. Is that --

DR. FALK: Well, it was just assumed that it would be a standard safety evaluation, but Carl would like to expand.

DR. FRASCH: As you must know, for a vaccine to be utilized by the FDA it has to be shown to be safe and effective. Okay? So the workshop dealt with the second of those two. Okay?

ACTING CHAIRMAN DAUM: Dr. Broome, Insel, Giebink, and I think we'll do open public hearing.

DR. BROOME: I was curious about whether you could give us a little more information about the correlation between opsonophagocytic assays and ELISA, and the variability based on serotype. In particular, was this of a magnitude which we really need to factor into our afternoon's discussions, i.e., you cannot make a generic statement about correlation?

DR. FALK: Without having reviewed the data before this meeting in such a way to be able to answer that specifically, the general consensus was that for some serotypes there appeared to be a better correlation.

There was also some -- but not necessarily -- we didn't have an opportunity to see whether that was true for which particular serotypes. I do not

recall those data in enough detail to feel comfortable presenting those in this forum, and I think that the fundamental take home message would be that the ability to demonstrate opsonophagocytic activity would be important whether there was -- you know, along the path to going to an ELISA endpoint, that needs to be factored in.

And, Carl, did you want to add to that?

It needs to be part of your I guess I would say clinical development program to support an ELISA endpoint, is to have this piece of data.

DR. FRASCH: I would only add to that in that there is a clear correlation between opsonophagocytic activity and ELISA. Now, these correlations are usually carried in R values, but it's not quite clear how good is good.

And the other point I would like to make is that these are two different assays, and the sensitivity of the assays are quite different, and so we cannot hope that the opsonic assay have the same sensitivity. It's simply not going to happen as the ELISA.

ACTING CHAIRMAN DAUM: Dr. Insel and then Dr. Giebink.

DR. INSEL: Two questions. The first with

respect to opsonophagocytic assays. Was there discussion as far as trying to make the assays more sensitive? Because what we heard today is under microgram per mL we're losing sensitivity.

Is there a movement on behalf of the community to make assays more sensitive? Was this discussed at the workshop?

DR. FALK: Well, on a very superficial level it was mentioned that there are some steps in that direction, such as agreement on using a particular cell line. So, you know, that's the level that they dealt with on that, but acknowledged that that was going -- you know, the ability to standardize that assay was going to be difficult, but there are some attempts.

But Carl is more of an expert on the ins and outs of exactly what those steps are.

DR. FRASCH: I think all I should add is that even strains within the same serotype vary in their ability to be opsonized. So the opsonic assay itself is reasonably well standardized now based on the publications that are coming out of CDC.

The problem is strain selection. There are some problems to be worked out, but we've been working on this for a good number of years.

DR. INSEL: The second question with respect to memory that was discussed at the workshop, it was proposed that there would be an important assay for memory, especially for serotypes where field efficacy has not been established.

And a very quick question is: does the polysaccharide, the 23-valent polysaccharide vaccine -- will it suffice for all of the serotypes that the different manufacturers are planning to incorporate in new vaccines? Are they all covered in the 23-valent vaccine?

DR. FRASCH: Yes, yes. There's been no proposals to include any types that are not presently in the 23-valent type.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Giebink, not least.

DR. GIEBINK: because the issues of extrapolating from a population outside the U.S. to the U.S. population are so important in the afternoon's discussion, even though we've been cautioned to be careful about extrapolating from Hib experience to pneumococcal experience, there was a lot learned about population differences in the late 1980s with Hib vaccines, and at least two of our committee members and Dr. Frasch have that information.

Was that discussed, Dr. Frasch in the historical portion of the meeting, those population differences?

DR. FRASCH: Yes, it was, and in addition, there was data presented on the response of Philippine children to exactly the same batch of pneumococcal conjugate as Finnish children.

And as you well known, the case in Chile and Venezuela with the hemophilus conjugate was pretty much what they saw with the pneumococcal conjugate in that there was a substantially higher response for reasons we are not quite clear about to the vaccines in those two populations than in the Finnish population and, I should say, in the U.S. population.

So this is one of the very strong caveats we have to consider when we're looking at efficacy trials in another country. Can the data actually be bridged to the United States?

ACTING CHAIRMAN DAUM: Thank you very much. I think we've had a very lively discussion and some fine presentations this morning.

We now need to move on to the open public hearing. Is there anyone that wishes to address the committee?

(No response.)

ACTING CHAIRMAN DAUM: In that case, we shall adjourn for lunch. It's 12:02 here in the Eastern time zone, and we will reassemble precisely at one o'clock.

Thank you.

(Whereupon, at 12:05 p.m., the hearing was recessed for lunch, to reconvene at 1:00 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:11 p.m.)

ACTING CHAIRMAN DAUM: Good afternoon and welcome back.

I trust everybody had a good lunch, not too big a lunch. We've arranged for that thumping that you heard this morning to occur at irregular intervals this afternoon should anyone nod off. We continue our upgrading to Holiday Inn Select.

We'd like to ask Dr. Gruber, please, to first put the items for discussion -- run through them again. Then we'll put the first one on the screen, but then we'll ask the committee to begin talking about whatever issues are of interest to put on the table to them. We'll have some free discussion like that for a while, and then eventually we will start focusing on the questions themselves.

So, Dr. Gruber, would you start us off, please?

DR. GRUBER: Yeah, thank you.

The first question is or the first item for discussion: please discuss whether or noninferiority immune response trials comparing a new pneumococcal conjugate vaccine with Prevnar are sufficient for inferring efficacy against invasive

disease for the new product. If so, what immunological parameter should be used?

And, number two, please discuss the criteria that should be considered to evaluate the serotypes not contained in Prevnar.

Number three, please consider the following scenario. An invasive disease efficacy study may be performed in a non-U.S. population with a new pneumococcal conjugate vaccine. If efficacy is demonstrated, could data derived from such a trial support licensure of the vaccine in the United States?

If so, what are the immunologic parameters that should be used to establish comparability to Prevnar in a U.S. bridging study?

And question number four, please discuss if data demonstrating clinical efficacy against acute otitis media for a new pneumococcal conjugate vaccine can always be used to infer efficacy against invasive pneumococcal disease for this new product.

And go back to slide number 19.

ACTING CHAIRMAN DAUM: Thank you very much, Dr. Gruber.

I'm going to leave item for discussion number one on the screen. We don't necessarily have to speak to that yet, depending on how the discussion

goes.

So who wants to start off? Dr. Kohl, then Dr. Griffin.

DR. KOHL: I have two questions that I'd love anybody in the room to answer. We know from published and maybe some unpublished work that there are otitis media efficacy trials, one that recently appeared in the New England Journal. Are there any serologic data that have emerged or that anyone here has from those trials that can help us in associating efficacy levels, immune correlates versus efficacies since the Prevnar trial for invasive disease has such a high efficacy that there's a very little amount of information we can actually gather from that.

ACTING CHAIRMAN DAUM: Anyone from FDA, do you want to tackle that? Dr. Frasch, I was looking for you.

DR. FRASCH: I would first caution us in that antibody values that we may get out of otitis media trial may not be directly translatable to invasive disease. So any discussion would have to consider that caveat.

ACTING CHAIRMAN DAUM: Having said that, is there information?

DR. FRASCH: I think one should ask some

of the actual players maybe in the room that worked on these trials.

ACTING CHAIRMAN DAUM: Okay. If that's the way we're going to go, then I guess I'd ask audience members to help out here. We will ask you to clarify or provide information about committee questions if there is information available. Is there someone in the audience who has information about this?

Dr. Siber.

Everybody who does so will have to state who they are and what their affiliation is.

DR. SIBER: George Siber, Wyeth.

We don't have information, but we can tell you the information that's likely to be forthcoming. In the Finnish trial sera were drawn on half of the cohort after the primary series, and on the other half after the booster dose, and those sera are being assayed or have been assayed, and the antibody levels seen in those sera will be correlated with the subsequent occurrence of type specific otitis media.

ACTING CHAIRMAN DAUM: Those data would be most valuable, I would think, in trying to sort out some of the issues here.

Dr. Giebink.

DR. GIEBINK: The only animal model that looks at both middle ear protection and invasive protection is the chinchilla model, and in that model using two different conjugate vaccines we have consistently seen across serotypes and across vaccines that antibody levels required for protecting the ear are considerably, not logrithmically, but in the neighborhood of two to fourfold higher than those levels required for protecting against bacteremic disease.

I don't know how you'd scale that to a human, but I obviously have my bias.

ACTING CHAIRMAN DAUM: Well, save it. We might like to hear your bias, but we'll ask Dr. Griffin next for comment.

DR. GRIFFIN: Okay. I don't have comments on this, although I'd certainly be interested in the answer.

ACTING CHAIRMAN DAUM: We're in free form here.

DR. GRIFFIN: Okay.

ACTING CHAIRMAN DAUM: For a while.

DR. GRIFFIN: Since this is not an area in which I work, I would be -- I would benefit from understanding better how the ELISA test particularly

is done.

Being sort of a fan of functional antibody assays and knowing that ELISA is basically going to give you binding antibody and is not going to tell you whether the binding is to the relevant portion of the antigen in question, first of all, I assume that they're done with purified polysaccharide as the antigen. Is there any way of knowing whether the antibody that's being measured as against the relevant part of the polysaccharide, which I assume is the part that's poking out on the surface of the bacterium?

ACTING CHAIRMAN DAUM: We will turn to Dr. Frasch first for response to that.

DR. FRASCH: Okay. We've been working with the World Health Organization with CDC sine 1993 in standardization of the ELISA assay. The ELISA assay uses purified pneumococcal polysaccharides that are obtained from the American type culture collection, which obtains vaccine quality polysaccharide from Merck. So, therefore, the polysaccharides used in the assay are the polysaccharides that pass the requirements for vaccine quality polysaccharide.

This said, due to the very nature of the pneumococcal polysaccharide, there are some other

contaminants unavoidably present, very small quantity, and there's an absorbent C-polysaccharide that's normally used by everybody and most everybody uses the same source. So that helps standardize the assay.

But, yes, the antibodies measured are antibodies that bind to the polysaccharide, and it is possible that some of those antibodies that bind are not functional.

Now, this has not been seen in sera from children, as we're talking about, today, but it has been seen in looking at sera from older individuals, elderly individuals. The ELISA measures quite a bit of nonfunctional antibody in that population, but today's discussion is with young children.

DR. GRIFFIN: Okay. One follow-up sort of technical question. When people are talking about measuring avidity or avidity of antibodies to these polysaccharides, are those assays ELISA based assays using urea washes or what, again, are we talking about specifically there?

DR. FRASCH: Again, that's essentially the same assay in which a kayotropic agent, usually sodium thiocyanate, but it could be urea, is used to either block initial binding of the antibody or to a loosely bound antibody, and having done the assay in our lab

both ways, we get very similar answers by either method, but basically it's using a kayotropic agent in exactly the same assay as used for normal quantitation of the antibodies.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Kim, please.

DR. KIM: I guess knowing that, these immunologic assays have not been standardized and variable, is there in your -- I guess these are two related issues. One, is there an attempt to have a reference serum which can be used by everybody to do everything, do the functional assays and the binding assays, everything, to see the degree of variation if that has not been discussed or has been discussed, then was there any actual performance of such assays being done with a serum which has been shared by all investigators or manufacturers, including CBER?

ACTING CHAIRMAN DAUM: Dr. Frasch, would you like to respond again?

DR. FRASCH: First of all, I've got to clarify something. It's not that the assays are not standardized with individual laboratories. Our work over these years has been to standardize assays between multiple, multiple laboratories.

Number two, there is a standard reference

serum supplied by the FDA to all interested parties throughout the world. It's called reference serum 89SF, and it has assigned values to each of the relevant serotypes, and we're also working on a set of what we will call calibration sera that can be shared among laboratories.

DR. KIM: Can I just have one follow-up?

ACTING CHAIRMAN DAUM: Sure.

DR. KIM: I have one follow-up question. Does that serum contain antibodies against the serotypes that are under discussion or serotypes have been limited?

DR. FRASCH: The origin of this serum was BPIG plasma, and if people remember what BPIG plasma is, this is from individuals who are immunized, adults that were immunized with the 23-valent pneumococcal polysaccharide antibody, and we now have antibodies quantitated to all 23 different types of which we're only really interested in about 11 of the types now.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Stephens.

DR. STEPHENS: I'd like to follow up on a question from Dr. Griffin and ask for comments about the avidity ELISA, which has been suggested both here and at the previous meeting as potentially being an

assay that can tell us -- that correlates better with opsonophagocytic activity, as well as also correlating with memory, and I just would like Carl's comments or other comments about the avidity ELISA and their thinking about that.

DR. FRASCH: Well, the data that was actually presented during the workshop did not really deal with avidity versus opsonic antibody, but it dealt with looking at something called avidity maturation after immunization with a conjugate versus a polysaccharide.

And basically what they found was that if you immunize with a polysaccharide, you really didn't see much increase in the avidity of the antibody over time, whereas with the conjugate just looking at the post dose three versus the pre-booster, one saw with the conjugate an increase in the avidity of the antibody, and some suggested at the workshop that this might be a good surrogate marker for memory.

ACTING CHAIRMAN DAUM: That is to say the presence of the high avidity antibody would be the surrogate, not any boosting capability.

Dr. Insel.

DR. INSEL: What is the basis for making that assumption? It may correlate, but all antibody

titers, avidity will increase for any T-dependent antigen with time. If you just wait long enough, things do increase, but does that speak directly to the fact that that host will respond to the isolated polysaccharide when presented? Are these just two different findings?

Do we know that that assumption is correct? Because avidity increases, you'll see responses to a polysaccharide vaccine in those prime cells?

DR. FRASCH: I mean, the problem is the same population you're studying shows the increase or avidity maturation and shows priming or a memory, but where they're one and the same event, the data wouldn't show that.

DR. STEPHENS: Just as a comment, I think there's reasonable data, and Carl or others may correct me, in the Haemophilus influenzae literature suggesting that there is a correlation between avidity maturation and memory responses in terms of polysaccharide challenge as another means of assessing memory.

I'll let others comment on that.

DR. INSEL: With hemophilus, I mean, you can prime probably in the absence of any avidity

maturation. They don't have to go hand in hand. I mean just the fact that even with one dose of conjugate vaccine you can prime for a polysaccharide response.

In fact, in Jani Eskola's (phonetic) data, where immunized in the newborn period, about 30 percent of those infants were primed to respond at four months of age to a dose of polysaccharide vaccine, and that was occurring probably even in the absence of any kind of evidence of avidity maturation per se.

I think they can go hand in hand, but I'm not sure that one necessarily follows the other, and the question is whether or not one needs to be looking at -- the question is whether one needs to be challenging with a polysaccharide, especially for the vaccine serotypes that we don't have field efficacy data on as we go forward here. I mean that's the question I'd just like to throw out to the group.

ACTING CHAIRMAN DAUM: Dr. Giebink.

DR. GIEBINK: Another subject. I'd like to elicit some discussion on the antibody threshold method that has been presented where the antibody concentrations in a vaccinated group are compared with those of an unvaccinated and the difference plotted.

You'll remember that graph.

I have two concerns with that method. The first is that in the studies I'm familiar with, there's an indirect relationship between the degree of the antibody response after vaccination and the pre-vaccination antibody concentration. The higher the pre-vax concentration, the lower the fold increase.

And, secondly, there are differences in antibody concentrations among populations in unvaccinated populations. We've compared, for example, a Minnesota population to a Columbia, South America population and found quite different concentrations to several different serotypes in these unvaccinated groups.

So both of those issues would bear on that methodology of drawing the difference, and I wonder. I just want to raise the question and see if others have thoughts.

ACTING CHAIRMAN DAUM: A comment on Dr. Giebink's question?

Dr. Gruber.

DR. GRUBER: Yeah, I would like to comment on that. When I presented this graph, that was really actually providing with a piece of history. So it was really an approach that we have been using to look at

the bridging, the manufacturing bridging that Wyeth had to do, looking at their commercial lot versus the pilot lot that was used in the efficacy study.

One might question, however, that a method that was used there would be even applicable to what is being discussed today since we may not have the situation that we have, an unimmunized individual there.

So what we may have to look at if we compare a new vaccine X with Prevnar is really looking at antibody concentrations induced by one vaccine versus the other, i.e., perhaps looking at reverse cumulative distribution curves.

I mean, I'm just throwing this out, but I doubt that the approach that we have used at that time is the exact approach that we will be able to use for the purpose of comparing the new vaccine to Prevnar.

ACTING CHAIRMAN DAUM: Scott, do you want to follow up on that?

Okay.

DR. GRIFFIN: Could I ask another question that's along this line?

ACTING CHAIRMAN DAUM: Certainly.

DR. GRIFFIN: Can somebody just give me an idea of the order of magnitude we're talking about

when we're talking about different baseline levels for Minnesota versus South America or even in the responses like in the Philippine children versus the Finnish children?

I don't know if we're talking about twofold, tenfold. You know, I just don't have an idea of the order of magnitude of differences that we're dealing with.

DR. GURUNATHAN: The Colombian Minnesota study, the biggest differences that we saw by serotype were in the neighborhood of two to threefold, and we speculated that that may have been due to serotype exposure because type 5 concentrations were quite high --

DR. GRIFFIN: That would make the most sense.

DR. GURUNATHAN: -- in Colombia and very low in Minnesota. I don't know about vaccine response.

ACTING CHAIRMAN DAUM: Before we call on Dr. Kohl and then Dr. Decker, Dr. Falk, do you remember, or Dr. Frasch, from the pneumococcal workshop there were some data presented there from the Philippines which were kind of striking? And do they bear on Dr. Griffin's question? But I can't remember

them.

DR. FALK: I unfortunately would not feel comfortable exactly quoting a fold difference, but I believe that they were striking in that we're looking at I think it was more the two to threefold increase, but I hesitate to say take that as gospel

ACTING CHAIRMAN DAUM: Dr. Frasch, do you want to deal with that issue?

DR. FRASCH: Well, that's pretty much the range, but the problem there is if we're trying to bridge to a U.S. population, and already the levels are two to threefold and we're allowing much less, so it makes bridging more problematic.

DR. GRIFFIN: I think that's sort of my point, you know, that it's very hard -- it becomes hard to sort of compare these populations.

DR. FRASCH: Yeah, that's why it's important to know the epidemiology of the population that you intend to do a trial in.

ACTING CHAIRMAN DAUM: Dr. Kohl and then Dr. Decker.

DR. KOHL: Could someone address these same issues on a more local level? That is to say what do we know about minority urban communities in this country, and can someone refresh my memory on the

Native American experience, which there was a considerable amount?

ACTING CHAIRMAN DAUM: Did anybody want to take that on, anybody at the table?

Is there anybody in the audience that can shed light on that?

DR. KIM: The only information that I have been informed of that is a serotype distribution differs in Native Americans compared to rest of the U.S. population. So that, I think, needs to be considered in looking to vaccines.

ACTING CHAIRMAN DAUM: Dr. Butler, I was hoping you would.

DR. BUTLER: Particularly in Alaska Natives and in the Navajo, serotype 1 is more common compared to non-Native populations in the United States, and I guess the next question then in terms of immune response, there's one study looking at the OMP vaccine that compared Alaska Natives, Navajo, and children in a Southern California HMO, which showed very little in the way of significant differences.

I think the response to the first does was somewhat attenuated in the Alaska Natives who had higher pre-vaccination antibody levels, but after completion of a primary series, there was practically

nothing in the way of significant differences.

ACTING CHAIRMAN DAUM: And that's the H. flu. OMP vaccine?

DR. BUTLER: No, that's the pneumococcal OMP vaccine. I will have to defer to someone from Merck to tell whether or not protocol 014 -- how that differs from the vaccines that they're most interested in now.

ACTING CHAIRMAN DAUM: Does anyone from Merck care to respond to that issue?

Okay. While we're doing that, perhaps we could hear from -- does anyone from Wyeth Lederle care to respond to the issue with respect to the Native American trial that is in advanced analysis now? Because that bears on this question also.

DR. KOHBERGER: With respect to the Native American pneumococcal data, the database has been clean, locked, and is to be sent to Johns Hopkins within the next two weeks. So the analysis is ongoing. So we really can't say anything about what those levels are yet. It will be several months.

ACTING CHAIRMAN DAUM: Several months? Too bad.

Okay. Dr. Decker and then Dr. Diaz.

Well, are you guys ready? All right.

Before Dr. Decker speaks, we will. You need to tell us who you are again.

DR. SILBER: Sure. Jeffrey Silber, Merck.

Maybe we could let Dr. Decker speak. I don't know how long this is going to take.

ACTING CHAIRMAN DAUM: It looks like it's real close.

All right. Dr. Decker.

DR. SILBER: Oh, here we go. Okay. This was protocol 14, a study conducted by Merck a number of years ago in which we looked at Native American, Native Alaskan, and general U.S. population infants. These are post dose three data. All children received Tetramune concomitantly, and for the purposes of this study, we look at a threshold level of 0.5 micrograms per mL. You see the sample sizes here.

And if we just want to focus perhaps on the geometric mean titers or the threshold responses for this particular lot of vaccine, the non-Native races across all serotypes trended toward having lower geometric means and sero-responses.

ACTING CHAIRMAN DAUM: And the assay here is?

DR. SILBER: This was a binding ELISA.

ACTING CHAIRMAN DAUM: Is it one that's

entered into the protocol -- I don't know what the right word is -- but the protocol standardization?

DR. SILBER: Oh, yes, our laboratory.

ACTING CHAIRMAN DAUM: And is that the same -- is that a vaccine you have in trial currently?

DR. SILBER: This formulation is not in -- this particular formulation is not in trial presently.

ACTING CHAIRMAN DAUM: Okay. Thank you.

I think now we will go to Dr. Decker. Thank you very much.

If you could, throw the first question back on the screen for us before you run off.

Michael.

DR. DECKER: You know, we have four questions with multiple sub-questions raising some very complicated issues, and I wonder if we can't simplify our approach a little bit by looking at some practical considerations that might weed out some of the underbrush.

For example, I assume that it's sufficiently a given good that this committee and the FDA would like to see other vaccines licensed and would like to see the number of serotypes increased so that we wouldn't adopt a stance that blocks either of those two approaches.

It seems to me also that if we said an efficacy trial had to be conducted for a serotype not in Prevnar, that we would understand we were, therefore, saying we did not expect to see additional serotypes added because if a company could come forward with a seven-valent identical to Prevnar and get licensed without an efficacy trial, but had to do an efficacy trial to license any additional serotypes, we would be putting a monumental barrier to the introduction of these additional serotypes.

So I think we're not likely to say that, and given the enormous difficulty of conducting an efficacy trial against Prevnar in terms of sample size, I think the slide earlier made it clear that it was impossible even with the very optimistic assumptions in the FDA slide.

Then I think as a practical matter we probably are recognizing that we're going to have to come up with a pathway to licensure other than efficacy trials, with serologic unless we can think of some third alternative.

And if we accept that, that there will be a serologic pathway to licensure, then I think that further simplifies things because if there will be a serologic pathway to licensure, then nobody is

obligated to go the efficacy trial route, although, of course, that would still be an option. And if there's a serologic pathway to licensure, there's no obligation to go into these populations overseas that have very different antibody responses to American kids raising all of those thorny issues.

It would seem to me that it would be possible then to do trials Prevnar versus new vaccine in the U.S. and moot a lot of these issues. Now, there may be holes in my chain of reasoning there, but if any of that holds up, then perhaps the practical questions in front of us are much simpler and more answerable than the theoretical questions, which are very difficult.

ACTING CHAIRMAN DAUM: Well, that's an interesting comment for us to think about. It really goes to discussion item one, and I'd like to sort of hold it in abeyance and have people consider it as a comment based on this discussion item, but continue some free form discussion until we focus on it, which will be soon.

Dr. Diaz, then Dr. Goldberg. Dr. Insel.

DR. DIAZ: Just following along on the thoughts that were raised about doing studies abroad, I think it's certainly clear to me that having a basic

understanding of the epidemiology of pneumococcus in any population that's going to be enrolled into any kind of clinical trials is really critical, especially when you talk about having to bridge perhaps trials overseas to the U.S., knowing for instance just the strains that cause -- that are more prevalent in terms of causing disease in those areas, perhaps even the prevalence of carriage of certain strains and preexisting antibody may all play a role in trying to or in complicating, I guess, any kind of bridging studies that would occur.

I know that in the United States there's a lot of data being collected regarding antibiotic resistance for pneumococcus, but I was curious if anyone knows if there's any data being collected perhaps in the ID sites or other places regarding prevalence of carriage of strains or any current epidemiology of pneumococcus other than invasive disease in this country.

ACTING CHAIRMAN DAUM: Are you talking about in places where vaccine is in use or --

DR. DIAZ: Just talking about in general looking at sort of what's going on with the epidemiology of carriage of strains in this country and those strains that are still causing diseases

being monitored. But I'm not sure if I have a good feeling of the epidemiology as it exists currently.

ACTING CHAIRMAN DAUM: Carl, do you want to respond to that? Are there post marketing things that were put into place with respect to carriage?

DR. FRASCH: Well, my interpretation was it wasn't necessarily following vaccine. So, therefore, I would ask Dr. Butler to.

DR. BUTLER: I'm not sure how well I can address the question for the country as a whole. We're actually doing quite a bit of that in Alaska in primarily two settings. One is the rural village setting where rates of disease are extremely high, building on a baseline of work that was done in an intervention of judicious antibiotic use, but it has provided three years of baseline data which we are continuing to collect data, basically looking at carriage across all age groups within 17 villages.

We also have a project specifically looking at the impact of, post marketing impact of conjugate vaccine in the Anchorage area, and that's really a broad population, Native, non-Native, also a public clinic population, looking primarily at preschool age children.

I suspect there are similar studies going

on in other communities in the U.S. thought.

ACTING CHAIRMAN DAUM: Scott, do you have data about Dr. Diaz's question?

DR. GIEBINK: Just to clarify, there are carriage studies going on at a number of sites in the United States, all related to the efficacy testing of new antimicrobial drugs for acute otitis media, and those actually -- a number of those studies were reported in town here about a month ago at a license application from one of these manufacturers.

So I don't have those at my fingertips, but it's pretty well known that resistance rates among pneumococci carried in the upper respiratory tract are considerably higher than the rates of resistance in invasive disease, and there's quite a bit of regional information in the United States available on that.

ACTING CHAIRMAN DAUM: Do any of the manufacturers, Wyeth, in particular, want to share any thoughts regarding carriage surveillance and places where the trials have been done?

(No response.)

ACTING CHAIRMAN DAUM: I take it that means no. Okay. Well, Dr. Diaz, I think that's a very good question. We just don't have a lot of light.

Dr. Decker, on this question?

DR. DECKER: Yeah.

ACTING CHAIRMAN DAUM: Because I have three people ahead of you.

DR. DECKER: No, an answer to this question if you want.

ACTING CHAIRMAN DAUM: Okay.

DR. DECKER: Out of a study reported in IDSA last year, supported by Wyeth Lederle and conducted by Kathy Edwards and colleagues at Vanderbilt looking at children who received Prevnar and who were followed very intensely for surveillance of carriage with an average of nearly a dozen cultures obtained during the first year of life, and let me just give you some key results here.

I can give you specific numbers, but in summary -- actually I said Prevnar, but it was the nine-valent vaccine -- carriage rates were extremely high, with carriage rates of, for example, pneumococcal isolates of over 80 percent in both the vaccine and the control group were resistant to penicillin among ill kids. Over 70 percent were resistant to penicillin among all kids.

The rates of carriage of vaccine strains were reduced both in well and ill kids, but still

relatively high, but statistically significantly reduced.

And one second here. Vaccine recipients were 19 percent less likely to carry the vaccine strains at well baby visits and 29 percent less likely to do so at sick visits, but there was no overall reduction of the carriage rate of all pneumococci and no reduction in the carriage rates of penicillin resistant strains.

I'm not sure if those data answer your question directly. If not, put it to me again because I may have the answer in here.

DR. DIAZ: That's fine.

ACTING CHAIRMAN DAUM: This is obviously a very complicated area that needs more light shed on it.

Dr. Siber, can you shed light?

DR. SIBER: Well, I'll tell you there will be some light coming from the Navajo trial which was a trial in which there was community randomization between the pneumococcal conjugate vaccine, Prevnar, and a meningococcal vaccine, and one of the sub-studies by Kate O'Brien in that study, together with CDC investigators, is to look at the herd immune impact of pneumococcal vaccine in a whole community of