FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Vaccines and Related Biological Products Advisory Committee

(Day One)

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Dr. Robert Daum
Dr. Thomas Fleming
Dr. Eric Hewlett
Dr. Wendy Keitel
Dr. Claire Broome
Dr. Theodore Eickhoff
Dr. Mary Glode
Dr. David Karzon
Dr. David Klein

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P R O C E E D I N G S [8:30 a.m.]

DR. FERRIERI: Will you please take your seats. We can start the session momentarily.

Agenda Item: Welcome, Announcements, Introductions

I am Dr. Patricia Ferrieri, chair of the Vaccines Advisory Committee.

We will start today with having a conflict of interest statement read by Nancy Cherry from FDA.

MS. CHERRY: Before I begin, I would like to make two announcements.

First of all -- I am afraid I will forget it later today -- those of you that are coming for the closed session tomorrow, I want to remind you that it starts at 8:00 not at 8:30 tomorrow.

The other announcement is that our sound is being picked up, I am told, by National Merit(?), so I just wanted you to be aware of that.

The conflict of interest statement is made a part of the record of this meeting of the Vaccines and Related Biological Products Advisory Committee on June 5th, 1997.

Pursuant to the authority granted under the committee charter, the director of FDA Center for Biologics

Evaluation and Research has appointed the following individuals as temporary voting members: Drs. Broome, Eickhoff, Glode, Fleming and Karzon and Snider for the discussion on the safety and efficacy of Haemophilus b conjugate reconstituted with acellular DTaP for infants -- that is topic 1 -- and the discussions on what types of data are needed in the future to approve adult pertussis vaccines, topic 2.

In addition, Dr. Hewlett has been appointed temporary voting member for the discussion on the safety and efficacy of acellular DTaP for infants, topic 1 but not for topic 2.

Based on the agenda made available, it has been determined that all financial interest in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee's discussion, which had been reported by the participating members, temporary voting members, consultants and guests as of this date, present no potential or an appearance of a conflict of interest at this meeting with the following notations and disclosures.

Dr. Adimora reported that in the past she was the principal investigator on an unrelated contract rewarded to

her employer by the sponsor of topic 2.

Dr. Apicella reported that he is the principal investigator on an unrelated grant supported by a firm, which could be affected by the discussions. The grant was awarded to his university. However, he receives a small remuneration.

Dr. Mary Lou Clements-Mann reported that she is the principal investigator on two unrelated grants supported by firms that could be affected by the committee discussions. She receives no remuneration. Also, she is listed as a consultant on an unrelated collaborative multi-center project with an affected firm. She receives no remuneration.

Mrs. Cole has disclosed that she was interviewed by the media for a special sponsored by a regulated firm. Also, during the conference she spoke on an unrelated topic and attended an awards dinner sponsored by the same firm. She received honoraria.

For Dr. Kathryn Edwards, a limited waiver was approved for the discussion on acellular DTaP in infants, topic 1. Dr. Edwards will not vote on this topic. In addition, Dr. Edwards has a narrowly limited waiver, which restricts her from participating in topic 2, the discussion

on adult pertussis. She may sit on the sidelines and answer questions put to her.

Also, the Agency approved a waiver on April 10th for a membership on the Data Safety Monitoring Board. Her membership is unrelated to the committee discussions.

Finally, Dr. Edwards is the principal investigator on an unrelated, unremunerated contract, supported by a firm that could be affected by the committee's discussion.

For Dr. Ferrieri, the Agency approved a waiver amendment on April 8th, 1997, for her financial holdings. The holdings remain unchanged.

Dr. Harry Greenberg, a former NIH employee, has reported that he is one of several NIH employees who hold two unrelated patents, which were licensed at NIH to a firm that could be affected by committee discussions. He has not received any income from these patents.

For Dr. Gregory Poland, a limited waiver was approved for related and unrelated contracts with the sponsor of topic 2 and a firm that could be affected by the discussions. In addition, Dr. Poland reported other unrelated contracts, including one under negotiation with firms that could be affected by the discussion of topic 1.

Also, Dr. Poland reported an unrelated grant, which receives outside funds from regulated firms to support the National Coalition for Adult Immunization, which he chairs.

Dr. Poland is limited to discussion only for topic 2. He will not vote on topic 2. There are no restrictions on his participation for topic 1.

Dr. Robert Breiman, a consultant, is employed by a federal agency, CDC, that could have an interest in the committee discussion because CDC purchases all types of vaccines for public use.

Dr. Claire Broome, a consultant, is employed by a federal agency, CDC, that could have an interest in the committee discussions because CDC purchases all types of vaccines for public use.

Dr. Robert Daum, a consultant, has a limited waiver restricting his participation in the discussions of topic 1, acellular DTaP in infants. He may sit on the sidelines and answer questions. However, he has been granted a limited waiver for related financial ties to the affected firms in topic 2, adult pertussis. Dr. Daum will not vote on topic 2, but he will join us at the table.

In addition, Dr. Daum reported past unrelated consulting to several regulated firms.

Dr. Theodore Eickhoff, a consultant, has been granted a waiver amendment for membership on the Data Safety Monitoring Board.

Dr. Tom Fleming, a consultant, reported that in the past he consulted with several regulated firms on unrelated subjects. He received a fee for his services.

Dr. Mimi Glode, a consultant, disclosed that she served as a moderator for a discussion on immunization, sponsored by a firm that could be affected by the committee discussions. No personal remuneration was received.

Dr. Eric Hewlett, a consultant, has been granted a limited waiver for topic 2 for a related contract, related consulting and indirectly related generic expert witness testimony. Dr. Hewlett will not vote on committee deliberations for topic 2.

In addition, the following was reported. Topic 1, an unrelated contract of unrelated generic expert witness activity. Also, Dr. Hewlett is involved in soliciting support from a number of regulated firms for the Borden Conference on Maturity(?) of Toxins and Pathogenesis. There are no restrictions on Dr. Hewlett's participation in topic 1 of the committee discussion.

Dr. Dixie Snider, a consultant, is employed by a

federal agency, CDC, could have an interest in the committee discussions. As part of Dr. Snider's official government duties, he is involved with government contracts for the purchase of all types of vaccines for public use.

In regard to FDA's invited guests and speakers, the Agency has determined that the services of these guests and speakers are essential. There are reported interests, which have been made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the applicant speakers.

The interests are as follows:

Dr. Wendy Keitel, a guest for topic 2, has received funding from an affected firm for unrelated research on pneumococcal and radius(?) vaccines.

Dr. David Klein, a guest for topic 2, is employed by NIAID, Division of Microbiology and Infectious Diseases. As part of his official duties, he works closely with the majority of pharmaceutical companies to help promote and advance candidate vaccines into the clinic.

These studies are conducted with NIAID's contract with vaccine and treatment evaluation units. As such, he is involved with a contract on the Swedish and Italian pertussis efficacy trials, as well as other various

agreements that support clinical trials.

The following participants did not have any financial interest to report: Drs. Evans(?) and Villalta.

Copies of all waiver statements and appearance determinations addressed in this announcement are available by written request under the Freedom of Information Act. Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in the event a controversy arises as a result of committee discussions.

In the event that the discussions involve specific products or firms not on the agenda, for which FDA's participants have a financial interest, that the participants are aware, they may exclude themselves from such involvement and that exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose products you wish to comment on.

That is the end of the conflict of interest statement.

DR. FERRIERI: Thank you very much, Nancy.

I would like to welcome again everyone here to

our sessions. We are in for a very interesting day, focused on one of our favorite organisms, Bordetella pertussis and the vaccines pertinent.

I would like to start by introducing everyone here at the table. If you could please start, Dr. Edwards, if you could introduce yourselves and your institution.

DR. EDWARDS: Good morning. My name is Kathy Edwards. I am a professor of pediatrics at Vanderbilt University.

DR. POLAND: Greg Poland, professor of medicine at the Mayo Clinic.

DR. CLEMENTS-MANN: Mary Lou Clements-Mann, professor at Johns Hopkins University School of Public Health.

DR. GREENBERG: Harry Greenberg, professor of medicine in microbiology and immunology at Stanford University.

DR. APICELLA: Mike Apicella, professor of microbiology at the University of Iowa.

MS. COLE: Rebecca Cole, consumer representative from Chapel Hill, North Carolina.

DR. VILLALTA: Fernando Villalta, professor, Division of Biomedical Sciences, Meharry Medical College.

DR. FLEMING: Tom Fleming, professor and chair, Department of Biostatistics, University of Washington.

DR. FERRIERI: Pat Ferrieri, professor of laboratory medicine and pathology and pediatrics, University of Minnesota, Minneapolis.

DR. KARZON: David Karzon, professor of pediatrics and microbiology at Vanderbilt University.

DR. HEWLETT: Eric Hewlett, professor of medicine and pharmacology, University of Virginia, Charlottesville.

DR. EICKHOFF: Ted Eickhoff, professor of medicine, University of Colorado.

DR. BREIMAN: I am Rob Breiman. I am director of the National Vaccine Program Office.

DR. FERRIERI: Thank you very much.

Agenda Item: Open Public Hearing

We move into the open public hearing then and we will start by a presentation from -- a request was made to us to present some data and Dr. Robert Colberger(?) will make the presentation, entitled "Theoretical Framework for Correlating Vaccine Immunogenicity and Efficacy."

Dr. Colberger.

Dr. Paradiza(?) is going to be the audio visual expert.

DR. COLBERGER: Peter has gone through a lot of training for this job and I just hope he does it well.

I obviously have a conflict of interest. I am not allowed to vote on anything, but what I want to do is present to you some data and some theory about work we are doing that takes correlative protection, population, immunogenicity or immunogenicity trials and combines it to determine vaccine efficacy. This is very similar to surrogate markers that we see in AIDS trials in CD-4 counts. And we haven't gotten involved in this very much in the vaccine area.

But we started to look at it. The reason, the motivation behind it was in our Erlangen(?) acellular trial, which you reviewed last fall. One of the jobs for the statisticians was to look at correlative protection. When we began to look at, it wasn't clear what correlative protection meant in vaccines.

As we worked on it, we realized that we could validate this protective model by predicting vaccine efficacy and comparing it to what we actually got in our real trial and, moreover, once we did this in pertussis, it would mean that in pertussis immunogenicity trials we would now be able to know what differences in GMTs really meant.

So, that is how we got motivated into this and it very definitely is a work in progress but I wanted to show you where we are headed with this and what kind of thinking we are doing.

After a lot of discussion with our immunologists and our clinicians about what mathematically is a correlative protection, we came up with this definition, that it is the probability of disease as some function of an immunologic response. So, that is nice and general. To get more specific, we are using a mathematical model called logistic regression and what it does is it takes a titer and predicts the probability of disease.

We are thinking primarily in sera IgG responses immediately after vaccination. In this equation that you see, it is E to the something divided by 1 plus E to the something. That something is A plus BT. A and B are constants, which you determine from the data and T is a titer. Now, it doesn't have to be a sera titer or just like that. You can take logs. You can have different immunological functions, depending on the science behind what is going on.

But using logistic regression because that y variable probability is constrained to be between 0 and 1

and that is what you get with logistic regression, in addition, it allows for a variety of different shapes of curves. I just want to show you some hypothetical models of protection that you can come up with. On the horizontal axis, it is titer and in this case it is the log scale. Probability of disease is on the vertical scale. So, for the graph on the right hand side, a titer of .1, your risk of disease then is approximately 95 percent.

If your titer is 1, the risk of disease is about 5 percent. That is what you get on the right hand side. And the shape of this curve is dependent on what values the constants A and B have, which, of course, comes from the data. So, it is a nice model to use. It is very rich in terms of obtaining different shapes of these correlates of protection.

Let's look at some real life data to see if this is a reasonable thing. This is from -- and I see Dr. White, I think she is in the audience, but it is from her paper on the Merck varicella vaccine. It has been adapted slightly by combining follow-up times. What we have here is the six week ELISA titer compared to the rate of VZV(?) infection and you can see that this could be fit by a logistic model, relatively horizontal at low titers and

then dramatically declining as your titers increase.

So, it may fit the varicella. The next slide hasn't been published anywhere. This is what we are working off. This is our Erlangen acellular pertussis trial, the household contact study. So, all these subjects have been exposed to pertussis and we know that from the household.

What we are plotting in a log scale are the four antibodies and vertically it is the percent of subjects with disease. What you can see is for PT and pertactin(?), it does seem to fit the logistic reasonably well and pertactin, except for that one empirical data point up here, it doesn't look so good, but a logistic curve could fit this data.

Now, we are resolving a lot of issues with this. But we are going to have to do multiple logistic. We need a multivariate model that puts the four antigens together into a protective model and they are all highly intercorrelated and it is a tough problem. This is one of the things we are working on.

The other thing you should realize and some of our scientists have told us, sometimes statisticians have to be reminded that correlation doesn't mean causation and

there is some discussion about whether these IgG values are really what is protective in pertussis. But that is another issue.

In any event, a logistic model to this kind of data seems to fit pretty well and we can estimate A and B for pertussis. Now, for pertussis, what does this mean? Well, it means that if we can get a correlate model, the next time we do immunogenicity trials, we are going to know what differences in GMTs really translate to in vaccine efficacy.

When you do this, there are some key assumptions we are making. The first is the disease follow-up interval. From when to when are we measuring diseases? And we have to be very careful about this so that we understand what that probability of disease really means.

The second point is timing of when we take the titer, when we are going to measure. In vaccinology, the most useful timing is probably immediately after vaccination or one month and we are assuming that antibody declines over time are similar in individuals and populations. There has been some work in waning immunity in vaccine efficacy by Bets Howard at Emory. At this point, we are not using that but that is an extension to

all those models.

Finally, there is the issue of correlation and causation because sera IgG values may not be what is important. However, I do want to point out that a logistic type model can be fit using other kinds of immune responses, but you do have to apply some immunology into this.

Now, once we have a protective model and we do our immunogenicity trials, what you can do is go from this correlative protection and immunogenicity and you can come up with an estimate of vaccine efficacy. Now, exactly how you do this is a subject of more statistics and math than I want to get into but conceptually what I would like to show you is this is a plausible protective model, logistic regression for, perhaps, H-flu. what you see is at a titer of 1. The probability of disease is .05. For .15 and below, the probability approaches 1. In between here, of course, is something we really don't know and this is what we are hypothesizing from logistic regression.

But it would seem obvious that if you are just slightly below 1, your risk of disease isn't 100 percent. It is something less than a hundred and it may increase as your titers go down. This is a typical immunogenicity

frequency distribution that you could see with anti-PRP titers. In this case, the GMT is 1 or the mean. It has got a standard deviation of 1.2. In actual practice, you can use whatever you get from the immunogenicity trial, whatever your particular trial gets in variability.

But the way you calculate vaccine efficacy conceptually is for each subject in your immunogenicity trial, you go up to the protective correlate model. You figure out the probability of disease. Then you average that over all subjects in the trial. So, you now have an average probability of disease; one minus that average divided by the probability of disease unprotected is vaccine efficacy.

That stuff has been submitted to a journal and it is pretty mathematical. I am not going to get into it.

For this particular example, here are three different titer distributions; one with a GMT of 1. You will note that 50 percent of them are above 1. Naturally, 50 percent are below. You obtain a vaccine efficacy of 77 percent, which is higher than that 50 and, of course, it is all dependent on this shape, this portion of that curve.

For a GMT of 4, vaccine efficacy is 92; vaccine efficacy is 97. Now, you realize there is a couple of

problems here. One is these are hypothetical curves. There is real life data that most manufacturers have on these immunogenicity trials and this curve is still relatively unknown. We don't know what it looks like primarily in this region, which is the key to vaccine efficacy.

Just to show you what happens to the percent of subjects achieving 1 in a GMT, there are 14 trials of our vaccines. We have multiple data points because these are multiple groups within each of these trials. And what you see is as your GMT declines, the percent of subjects achieving a titer of 1 declines also.

This is true from statistical principles. I mean, it has got to happen if you have a log normal distribution or any kind of a distribution, but the empirical data also supports it. Basically, what you see here is that a twofold GMT reduction results in a 10 percent decrease in percent of subjects achieving 1.

Now, we can tie all this together. The last slide showed that I can go from a GMT to a percent of subjects achieving 1 and the one before it showed how I can go from a GMT to vaccine efficacy. So, this completes the picture and what we can see here is in this range of GMTs,

this is what happens to the percent of subjects achieving 1; that is, you get around 4 or so. There is a big drop off in percent of subjects achieving 1. This is predictable from a normal distribution.

Vaccine efficacy also drops off like that. So, this is a tie-in of GMTs and vaccine efficacies. Now, there are a couple of assumptions we are making here and you have to be very careful about it. The major one is that population risk curve, which is still unknown.

What conclusions can we make from this? First of all, using percent of subjects achieving 1 is a reasonable estimate as long as it is a high percentage. However, it may be a conservative estimate and the degree of conservatism depends on what GMT you are dealing with and the steepness of this unknown protective curve.

We have to ask ourselves how well is 1.1 known. Is that really a good value? How well have we measured the GMT in terms of confidence limits and so on? Now, how can we use this? What can we use this whole framework for?

As I mentioned before, in pertussis we can use this now for our pertussis immunogenicity trials to look at what changes in GMT really mean. In H-flu it is really dependent on determining what that model is. We know that

as GMT declines, percent of subjects achieving so-called protective level of 1 declines.

We also know vaccine efficacy declines in this model, but the real question is, well, how much does it decline. In the absence of some agreed-upon protective curve, we really don't know how much vaccine efficacy declines, but we could figure it out if we had that model.

So, what we have done, we have tried to do, is provide some theoretical framework into tying all these things together so that we perhaps we are going to be able to really use surrogate markers in our vaccine trials.

If you have time, if you have any questions, I would be happy to answer anything.

DR. FERRIERI: Thank you.

Any brief comments before we move into our open session? Dr. Fleming.

DR. FLEMING: I think one of the key points that you had made in your discussion is the issue that correlation does not establish causality or a causal relationship. The kinds of considerations that you are giving are certainly very important. I believe they take the first step. It is a major task to establish ultimately whether or not these immune responses are not just

correlates but are truly surrogates.

It is an issue that has been considered at enormous length in this area and in other areas, as well. Specifically, there are a large number of types of immune responses and you are building models looking at certain of these immune responses in a very logical way. The models that you are building are really addressing whether or not, let's say, FHA changes are correlated with outcomes, with risk of infection.

One key point, as you note, is that when you see such a correlation, it doesn't specifically mean that you have established causality. My bigger concerns, though, go well beyond that and that is there are many different types of immune responses that can be occurring and the ultimate effect of a vaccine on risk of infection may not be at all adequately addressed by single types of immune responses that are being measured.

Ultimately, there are many intended, as well as unintended effects of vaccines and those unintended effects are often not anticipated, not recognized, not documented, so that as is the case with other potential correlates that could be used as surrogates in other disease settings, there is a great risk that you could be significantly

misled by a correlate thinking that it truly is a surrogate.

It may well be that in a given data set we can show with logistic regression modeling, which is a very logical thing to do, as you were doing, that as you increase FHA response or PT response within a given study, you will see a reduced risk or rate of infection and, yet, when you look across two vaccines, you may not find that improving the antibody response, FHA or PT, correlates or truly predicts the ultimate protective value of vaccines.

A simple example, and we may be coming back to this example repeatedly in the next two days, was from the acellular pertussis 1992 Sweden trial involving 10,000 participants randomized to four arms, where there was the two component acellular pertussis and then there was the five component acellular pertussis vaccine. The PT and FHA responses were much higher in the two component than the five component and, yet, the overall level of protection was 85 percent in the five component and only 58 percent in the two component.

So, even though within a given study you may well see with this very elegant logistic regression modeling, a correlation within the study for increasing protection with

increasing levels of antibody response of a certain type. Unfortunately, that doesn't tell us whether or not we can use that type of immune response as an end point or as a predictor and this has been the major shortfall of surrogates.

Ultimately, the first step in being able to get your foot in the door as to whether any kind of an immune response or biological response is a surrogate is to show that it is a correlate, but repeatedly in clinical literature, we have seen that correlates, in fact, are not validated surrogates.

So, I guess my last point is one of terminology. When we do these types of studies and we come back to your very first point, which is to say we are looking only at correlations and not truly a causality, I have a concern with the use of the term "correlate of protection," because I think we often think of that as vaccine-induced protection. There is almost an implied sense of causality. We are not looking at causality here. We are only looking at statistical correlations.

You have defined this as probability of disease as some function of immune response. I might have preferred a term "correlate of disease risk" because that

is really what you are looking at in these types of analyses.

DR. COLBERGER: Could I just make one brief comment and then I will --

DR. FERRIERI: Very brief, please.

DR. COLBERGER: You are absolutely right, Tom. Of course, we realize that. One of the things we are talking about with some of our NIH colleagues and academic colleagues is organizing a workshop with NIH to talk about this specifically with the vaccines sometime in September.

One of the things we were thinking of doing and seeing if we can do this, I don't know, is fitting our correlates model to the Wyeth-Lederle data, which, which has four antigens; then taking a look at the Swedish data and applying it to the vaccines with one, two and three antigens and seeing whether it validates or not.

I think if we can do that and get the cooperation among everybody to share data like that, we are closer to a surrogate than we were with just the correlate. So, we are trying to get a workshop together to do this and we will see.

DR. FLEMING: Just one real quick -- I strongly endorse that because ultimately what an extensive amount of

recent research in surrogates has shown is that to begin -- to really begin to understand whether a correlate could be a surrogate requires meta-analyses and data sharing and major joint workshops just in the manner that you have described.

DR. FERRIERI: We will have the opportunity to rethink these concepts as we deal with the meat of the day.

We have one other item in the open public hearing that we are aware of and Mrs. Cherry will read a letter that we received.

MS. CHERRY: Before I do that, is there anyone in the audience that wishes to make a presentation or a talk? This is the open public hearing session.

There will be one other speaker later in the morning, who couldn't be hear this morning, but seeing no one in the audience, then I will read a letter. I was asked by Chiron to read this letter.

It is addressed to me, Nancy Cherry, Executive Secretary, Scientific Advisors and Consultant Staff, CBER, FDA, from James Morton(?), M.D., MPH. And I am told that he is with Health Partners in Minneapolis. Dated June 3rd, 1997, regarding immunization of adolescents against pertussis.

"I am the principal investigator in a CDC-sponsored study of pertussis in adolescents and adults. We have recently completed the data acquisition phase of that study. An interim analysis of the data was presented last fall to the NIH group, which is planning an efficacy study of pertussis in adults.

"A partial analysis of the final data was presented recently in Washington, D.C., at the Society for Pediatric Research. Both presentations documented that we have found a substantial amount of pertussis in adolescents and adults, but especially in adolescents. Many of the cases were positive by culture or PCR. Depending on the interpretation of serologic data, the interim analysis last fall demonstrated an annual incidence of slightly above or below 1 percent with a somewhat higher rate in adolescents.

"These cases were diagnosed in patients who met the following criteria: They had been coughing from one to four weeks or had been coughing for less than a week, but had post-tussive emesis and they had no other obvious explanation for the cough, such as sinusitis, pneumonia or COPD and they had decided that they were sick enough to see a doctor.

"One of the main reasons our group applied for

this project was the substantial amount of pertussis seen in adolescents in Health Partners in the couple of years preceding this study. I have personally diagnosed four family clusters of cases in the year preceding this study. All four index cases were in adolescents. This had prompted us to do an informal study to see if this was common and, indeed, we found pertussis in adolescents.

"Dr. Kathy Edwards and her group have published data from a serologic study looking at PT, at adolescents and adults. This demonstrates a moderate peak in the GMT to pertussis at age 5, a large peak in adolescents centered on age 13 and a smaller but significant peak in the forties.

"The Minnesota Department of Health provisional data for 1996 demonstrates a continuing rise for pertussis occurring in adolescents. Out of the 433 cases, 30 percent were in children age 5 to 12 years; 6.2 percent were in children age 13 to 17 years and 20 percent were in people 18 years and older. Thus, in Minnesota in 1996, over half the reported cases of pertussis occurred in older children, adolescents and adults.

"Taking all these data and other published reports as a whole, I believe it supports the following

hypothesis about the epidemiology of pertussis. Pertussis circulates in substantial levels in adolescents. It certainly occurs in epidemics, but I believe it is also endemic in this age group. In the post-vaccine era, I believe that adolescents and to some extent adults who are no longer immune to pertussis form the reservoir for the disease.

"Thus, I strongly agree with the presentation, which Dr. Edwards made at the SPR this spring in Washington, D.C. The thrust of her presentation was a support of the thesis that the time has come to start immunizing adolescents against pertussis. I believe we should proceed down this path as rapidly as we safely can. To do so will save substantial morbidity and some mortality."

That is the end of the open public hearing session for now.

DR. FERRIERI: Thank you very much.

We will move on then into Session 1, entitled "Tripedia used to Reconstitute ActHIB (TriHIBit) for Infant Indication" and I would like to turn it over to Dr. Carl Frasch from FDA CBER, who will introduce the topic and do the FDA presentation.

Carl.

Agenda Item: Introduction and FDA Presentation

DR. FRASCH: As you know, we have a license application before us from Pasteur Merieux Connaught. I will make some brief comments regarding the FDA position. The company will then make a presentation and then I will present the questions that we would like the committee to consider following the company presentation.

So, what I would like to do is begin with my presentation.

Now, Pasteur Merieux Connaught from Lyon, France, manufactures the Haemophilus b conjugate vaccine, ActHIB. This vaccine is a lyophilized product and may be reconstituted with Tripedia. Tripedia is an acellular pertussis containing DTaP vaccine manufactured by Pasteur Merieux Connaught, Swiftwater. The pertussis components are pertussis toxin or PT and filamentous hemagglutinin or FHA.

Both ActHIB and Tripedia are currently licensed for use in infants. In September 1996, the FDA approved use of Tripedia to reconstitute ActHIB for use as the fourth dose of DTaP and as a booster dose for Haemophilus b conjugate vaccine in toddlers. The present application is

to for ActHIB reconstituted with Tripedia, a combination vaccine that the company has identified as TriHIBit, to be used for immunization of infants beginning at approximately two months of age.

Now combination vaccines have become very important in recent years with the additional vaccines now recommended for routine immunization. ActHIB reconstituted with whole cell DTP is approved for infant administration, but the use of whole cell DTaP vaccines could be phased out in the U.S. Thus, we really need to think about replacement combination vaccines.

Of major importance was for Pasteur Merieux Connaught to show that the combination of ActHIB and Tripedia through reconstitution, when administered to infants at two, four and six months of age was safe and did not adversely affect the immune response to any other vaccine components, including diphtheria, tetanus, the two pertussis components and the Haemophilus polysaccharide.

From the standpoint of safety, the combined vaccine was administered to approximately 4,400 infants. Now, since the company is going to make a considerable presentation on safety, I will simply say that the FDA found no clinically relevant differences in the safety

profile of the combined vaccine compared to administration of the two vaccines in separate limbs.

There were three studies, only the first of which was designed as an immunogenicity study but all of which, of course, contributed safety data. Now, there has been a number of reports and publications showing that interference can occur when a Haemophilus b conjugate vaccine is combined with a DTaP vaccine. The FDA cannot ignore these points.

The purpose of this slide is to illustrate the magnitude of the differences that may be seen between separate and combined administration of a DTaP vaccine and Hib conjugate. Although the Hib vaccine used in these studies was not ActHIB, there is a very clear suppression in the immune response to the b polysaccharide, going from 50 percent seroconversion to 1 microgram, to about 55 percent seroconversion simply by combining the two products.

Thus, with these concerns among the health professionals for reduced potency of Haemophilus b conjugate vaccines when combined with an acellular pertussis containing vaccine, it is clear that Pasteur Merieux Connaught must clearly demonstrate that their DTaP

Haemophilus b conjugate vaccine combination does not result in a reduced immune response compared to the two vaccines given separately.

Randomized control studies by Pasteur Merieux Connaught were designed to demonstrate equivalence in immune response to all vaccine components when ActHIB and Tripedia were administered as separate sites or combined in randomized trials.

The company's immunogenicity study comparing separate versus combined administration in 144 infants showed that the geometric mean antibody concentration to the Haemophilus polysaccharide was significantly higher when the vaccines were administered separately, while no such differences were seen in any of the other vaccine components. However, the observed 85 percent seroconversion seen for the combined vaccine is consistent with historical data, as represented in the current package insert, which range from 83 percent to 97 percent in four different studies.

Based on our concern for possible vaccine interferences, we asked that the company provide antibody data from a second independent clinical study. As the clinical trials were originally designed, only Trial 468-01

was the antibody data to be collected. This trial was conducted at four study sites. Another much larger randomized trial, 468-08, was underway for comparative safety. This trial was conducted in many more sites with a coast-to-coast representation of the U.S. population.

The FDA asked that the study be modified to collect post third dose serum samples for antibody studies. Since protective effects of the immunization are not considered until completion of the three dose immunization series, pre-immunization sera were not necessary. Although the pertussis responses have usually or traditionally been measured as fold increases, the confounding effects of maternal antibodies on the two month pre-immunization sera make fold responses difficult to interpret; thus, the additional sera would also be quite valuable for the pertussis responses I will discuss in a moment.

Now, in the case of the anti-Haemophilus responses, the important measure is not only the geometric mean response, but the percent of children with levels, antibody levels, predictive of long term protection; namely 1 microgram or more. Now, the data is shown briefly in the next slide. Shown here are the antibody results from 220 children, randomized to receive the vaccines combined or

given separately. In this study, the antibody concentration for the separate versus combined were not statistically different nor were there seroconversion rates to 1 microgram.

The other concern of the FDA was for the comparative immune responses to the two pertussis vaccine components in combination; pertussis toxin and FHA. Unlike Haemophilus, there is no correlation between a given antibody level to either PT or FHA and protection against whooping cough. Furthermore, the acellular pertussis efficacy trials were not done in combination with Haemophilus vaccines.

Thus, it was critical that the antibody responses to PT and FHA be shown to be equivalent whether DTaP was administered separately or as TriHIBit.

This slide presents some of the information regarding efficacy of acellular pertussis vaccines. As I mentioned, there is no clinical laboratory correlate or efficacy. Immunogenicity is used as a marker for positive interference and efficacy of acellular pertussis components in combination vaccines is supported by demonstrating no substantial reduction in response with a combined product versus a product shown to be efficacious.

Here are some considerations that we should have for evaluation of pertussis immune studies. They should be a direct comparison between combined vaccine and separate vaccines in the same study, same immunization study, the same component vaccine lots, randomization enrollments and I should add randomization and blinding of the antibody response measurements. The measurements should be for all the pertussis antigens; in this case, PT and FHA. And the sample should be assayed in the same laboratory using appropriately controlled methods.

Now, in regard to the pertussis antibody studies, the study 468-08 met all these criteria, while in our estimation the 468-01 antibody data for pertussis did not meet these criteria. Therefore, for its evaluation, the FDA used primarily the data from 468-08 as their primary analysis set.

Although there was some concern for assay standardization for estimation of pertussis antibodies, the clinical studies were randomized and the randomization and blinding extended to the laboratory personnel. Thus, any possible irregularities in antibody measurements in either 468-01 or 468-08 study would equally affect separate and combined administration.

We saw no differences in the immune responses to PT and FHA. Now, a very useful way to compare these responses is to plot the antibody data separate versus combined in something called a reverse cumulative distribution curve.

The next slide shows an example of such a curve in which we plot the percentage of subjects. Of course, at a very low antibody level all the subjects have this antibody level and out to a very high level where none of these subjects have this. And the important thing is that the two curves are very similar all the way along their distribution.

Now, I have no further comments. If there is any immediate question regarding my presentation, I will be glad to take it. As I said, I will present the questions afterwards.

DR. FERRIERI: Are there questions for Dr. Frasch?

Thank you very much.

Tom.

DR. FLEMING: Could you quickly clarify a couple of comments you made on -- about your second and third to the last slide, Slides 6 and 7, first on Slide 7 where you

give considerations in evaluation of pertussis immunogenicity studies. Just quickly you had mentioned that the 08 study satisfies these criteria; the 01 study does not.

In a sentence or two, the essence of your concern with the 01 study?

DR. FRASCH: Okay. At the point the 01 studies were being run, we had some problems with the assay validation for the two ELISA assays, the ELISA assay for pertussis toxin and the ELISA assay for FHA. Therefore, we looked strongly at the Chosel(?) data for 01, but we reserved our major consideration for 08. By the time -- first of all, as you know, we had the data in hand for the 01 study and then only at that point we asked them to collect the data from their ongoing 08 study.

Therefore, in the time interval between having done the 01 analysis and beginning the 08 analysis, the company had satisfied all of our concerns regarding the validation and ability to do the ELISA assays. So, therefore, we chose to choose the 08 as a primary data analysis for the pertussis. This has nothing to do with Haemophilus or the other antigens, only pertussis.

DR. FLEMING: The second question, you had stated

in your slide 6, there is no clinical or laboratory correlative efficacy and then immunogenicity used as a marker for possible interference. Can you add a couple of sentences on that? I mean, what is the basis for those two statements?

DR. FRASCH: Okay. I think Dr. Colberger mentioned that a little bit. The point is we have no firm correlate of which antibody correlates best with protection against pertussis and, therefore, since our only possible measurements at this point are antibody measurements, we must be very careful to see that there is no difference in the antibodies being induced when the vaccines are given separately versus combined.

This is one of the reasons why we were looking not only at the -- simply the fold responses, the GMTs, but also at the reverse cumulative distribution curves to look at all segments of the immune response, levels of the immune response.

DR. FERRIERI: Dr. Edwards.

DR. EDWARDS: Might it have been possible with a validated assay to reassay the samples from 01 to get the information that you needed?

DR. FRASCH: Yes. As you can imagine, the

company was asked to do assays and they will have more explanation on this than we will, but, in essence, they were asked to do many different assays and by the time they had completed the assays on the 01, some of the sera were exhausted. So, therefore, we were concerned about whether there was any bias in the sera that were used up versus available for reanalysis.

Since they started fresh at 08, all the sera collected were analyzed. So, that was another reason why we did not look strongly at the reanalysis of the 01 data, although, again, the 01 data, as they had analyzed it, showed there was no difference in their pertussis responses.

DR. KARZON: It would be useful to know the mechanism of the Hib response because in the future we won't know whether it is lot to lot in terms of preparation of material or whether it is an adjuvant or some other processing effect, so that we can anticipate and predict and maintain all products to be non-suppressive when they are combined.

DR. FRASCH: Yes. I think you voice a universal concern.

DR. FRASCH: Thank you. We will move on.

We will now go to the sponsor's presentation from Pasteur Merieux Connaught and the speakers will be Dr. Jim Williams, director of regulatory affairs, followed by Emmanuel -- Dr. Emmanuel Vidor, director of clinical research.

Dr. Williams.

I would like to remind everyone that we will adhere to our schedule and this will permit a more comprehensive discussion then as we move into the questions from FDA.

Agenda Item: Sponsor's Presentation

DR. WILLIAMS: Thank you very much.

On behalf of Pasteur Merieux Connaught, I would like to thank the FDA and the advisory committee for the opportunity to present data on the immunogenicity and safety of TriHIBit, our combination vaccine that was just described by Dr. Frasch.

The vaccine is composed of Tripedia, which contains pertussis toxoid, filamentous hemagglutinin and diphtheria toxoid and tetanus toxoid. PT and FHA are manufactured as concentrates and shipped to CLI by Beacon(?), Osaka, Japan. Diphtheria toxoids and tetanus toxoids are manufactured at Connaught Labs and they are

formulated with FHA and DPT, filled, labeled and distributed by Connaught Labs.

ActHIB is manufactured by Pasteur Merieux Sera Vaccines in France. It is composed of the purified capsular polysaccharide of Haemophilus b antigen conjugated to tetanus toxoid. Tripedia is used to reconstitute lyophilized ActHIB to give a .5 mL dose and this vaccine is given immediately after reconstitution.

The licensing status of the component vaccines for TriHIBit: ActHIB was licensed in the U.S. in March of 1993 and roughly 1.4 million doses have been distributed. ActHIB has also been used to reconstitute DTP -- I am sorry -- DTP has been used to reconstitute ActHIB. It was licensed in November 1993 and approximately 10 million doses have been distributed.

Tripedia was licensed for the fourth and fifth dose in August of 1992 and it was licensed for primary immunization in July of 1996. Roughly, 17.2 million doses have been distributed.

TriHIBit, licensed for the fourth dose in September 1996 and roughly, 200,000 doses have been distributed.

PLA was submitted in June of 1996 for TriHIBit

infant indication.

I would now like to turn the podium over to Dr. Emmanuel Vidor to discuss safety and immunogenicity for TriHIBit.

DR. VIDOR: Thank you, Jim.

It is a great pleasure to be here this morning and to have the opportunity to review with you all the safety and immunogenicity data we have got during the clinical development of this combination vaccine.

My presentation will give you first the review of the safety data for the TriHIBit vaccine given at two, four and six months of age, then followed by the safety data for the fourth dose given between 15 and 20 months of age. Then I will move on again for the immunogenicity data for this combination vaccine given at two, four and six months of age and then I will conclude on some of the preliminary data we have got for the fourth dose of this combination vaccine.

Five clinical studies have been done to address all these issues. The first one was safety and immunogenicity study, which compared three different lots of TriHIBit vaccine to ActHIB and Tripedia given at separate sites.

The second study was a large scale comparative safety evaluation between TriHIBit and Tripedia and ActHIB given at separate sites.

The third study was a non-comparative, large scale safety evaluation of TriHIBit and an amendment of this study, as I told you previously, Dr. Frasch, allowed us to generate additional post-immunogenicity data at post-dose 3.

The last study was safety and immunogenicity evaluation of the fourth dose of TriHIBit.

Safety: The first main safety study was a safety comparison between TriHIBit and Tripedia and ActHIB given at separate sites. Basically, nearly 2,600 infants two months old were enrolled to receive three vaccines at two, four and six months of age. It was a controlled, randomized, comparative study involving 30 centers all across the U.S.

Basically, infants were randomized using a three to one ratio into four groups. The first -- into two groups -- the first group was the combination vaccine, TriHIBit, and the second group was the two vaccines given at separate sites. Safety evaluation was done during the first three days after each vaccine dose and adverse events

and hospitalizations were collected up to 30 days after the last vaccination.

On this slide, I presented the results of the safety profile. Where you have on the first column the definition of the different events with for the three doses, the results and for each group, you have here the TriHIBit and the separate vaccines where are presented both the local reactions for Tripedia and the local reactions for the ActHIB site.

As the Tripedia site was considered as the most reactogenic, only the statistical comparison between the TriHIBit site, next is the Tripedia site, our presented at the bottom of this table.

The safety profile, the local safety profile, observed for TriHIBit was not different from the separate injection groups with the exception of the tenderness, which was slightly more frequent after TriHIBit, after dose 1, and for local pain, which was less frequent with TriHIBit after dose 2.

You have here the results from the systemic reactions, which are listed here. No increase of reaction rates were observed between dose 1 and dose 2 with the exception of low grade fever, which presented a slight

increase between dose 1 and dose 3, an increase, which was considered as not clinically significant; fever between 39 to 39.9 were less frequent for the TriHIBit group at dose 1 and persistent cry were less frequent with TriHIBit at dose 3. During this trial, no hypotonic-hyporesponsive episodes was observed.

The second safety study was a descriptive, large scale safety study involving nearly 2,800 infants two months old. Will receive again at three doses of TriHIBit at two, four and six months of age. It was an open label study involving 11 centers and similarly to the previous study, the safety was evaluated using the same criteria.

On this slide, I have presented the local safety profile for the TriHIBit vaccine at two, four and six months of age. As you can see, this local safety profile is quite similar to the safety profile observed during the previous study. A trend to observe, with the exception of erythema less than one inch, a trend to observe a decrease of reaction rates between dose 1 and dose 3 was observed and this trend reached statistically significance for swelling, tenderness and pain.

The systemic reaction profile was, again, quite similar to the systemic profile observed during the

previous study. With the exception of low grade fever, which presented a slight increase between dose 1 and dose 3, increase considered as clinically non-significant, some of the other reactions, like irritability and tiredness, presented a decrease between dose 1 and dose 3.

Again, no hypotonic-hyporesponsive episodes were observed during this study.

To conclude on safety of TriHIBit given at two, four and six months of age, more than 4,300 infants have received TriHIBit at two, four and six months of age and more than 12,000 injections were documented and a similar safety profile for TriHIBit was observed when compared to ActHIB and Tripedia given at separate sites.

A third safety study allowed us to document the safety profile of this combination vaccine, given as a booster dose to children primed with TriHIBit. Basically, 15 to 20 months children, who are previously immunized with three doses of TriHIBit, received a booster dose again of TriHIBit. It was allowed to give MMR and varicella vaccines at the same time on an open basis.

This study was open, descriptive and involved six centers. Again, the safety was evaluated using the same criteria.

Two hundred and four children were enrolled and you have presented here the local reactions observed for this booster injection of TriHIBit. When this local reaction profile is compared to the local reactions, which were observed during the primary -- the first phase of the study, you can see that the reaction rates observed for this booster dose are quite similar to the reactions which were observed after the third dose of TriHIBit, with perhaps the exception of erythema high of one inch, which were, in fact, very close to the rates observed after the first dose of TriHIBit.

Here are presented the systemic reactions, which were observed for the booster dose of TriHIBit and, again, when they are presented in parallel to the systemic reactions, which were observed during the first phase of the study, the systemic -- the rates of reactions were very close to the rates which were observed for the third dose of TriHIBit.

To conclude on the safety of TriHIBit given as a booster dose to children primed with TriHIBit, TriHIBit given at the fourth dose in toddlers primed with three doses of TriHIBit is as well-tolerated as ActHIB and Tripedia given in toddlers. And no clinically relevant

variation of reaction rates were observed between dose 1 and dose 4.

Let's move on now on the immunogenicity data we have got during these studies. To assess the immune responses to all antigens, we have found the different assays, which are listed on this slide.

Regarding the evaluation of immune responses to PRP and in order to provide additional data on the quality of the immune response to PRP, we have found some IgG subclass analysis and bactericidal activity analysis of vaccine-induced sera.

So, as some infants received at the same time hepatitis B and OPV vaccine, we have also evaluated the immune responses to these vaccine antigens. The endpoints used to describe the immune responses were classical with the expression of the germ mean titers and the percentages of subjects reaching short and long term protective levels.

For PT and FHA, we used the GMTs and the percentages of subjects with rise in their antibody titer. Diphtheria and tetanus were expressed as GMTs in units and equivalents per mL and also the percentages of infants reaching the levels of 0.01 units equivalent per mL and for hepatitis B and poliovirus antigens, we used either GMTs in

mini international units and seroneutralizing titers in dilution.

The first immunogenicity study enrolled two months old infants will receive vaccines at two, four and six months of age. It was a controlled, randomized and comparative study involving four centers. In all four centers infants were enrolled using a three to one ratio into four groups. In the first three groups infants received three different lots of Tripedia, A, B and C, used to reconstitute three different lots of ActHIB, 1, 2 and 3.

In the fourth group, infants received one of the Tripedia, lot a, given at a separate site to one of the ActHIB lot, lot 1. Immune responses were evaluated before and one month after the third vaccine.

On this slide are presented the immune responses to PRP after the third vaccination for the three combination lots. The overall GMT was 4.9 micrograms per milliliter with 95 percent of infants reaching the short term protective level and nearly 85 percent of infants reaching the long term protective level.

One of the lot gave a higher immune response compared to the two others. When one of the three combination lot was compared to the corresponding vaccines

given at separate sites, the immune response to PRP were higher in the separate vaccine group compared to the combination group. And the GMTs were different and also the percentages of infants reaching both protective levels.

The immune responses observed for the vaccine given at separate sites were in the upper limit of the range of expected responses we normally see with the PRPT vaccine. Also, we considered these differences as clinically non-significant. Finally, the level of immune response observed in the combination group were consistent with historical values.

To support these, you have on this slide a review of results obtained with the ActHIB vaccine, PRPT, given at two, four and six months of age in the U.S. during the different studies, which supported the U.S. licensure of the ActHIB vaccine. As you can see, the post -- the GMT after three doses of the ActHIB vaccine ranged from 2.6 up to 10.8 micrograms per mL and the short term protective level ranged from 96 up to 100 and the long term protective level ranged from 75 up to 97.

Similarly, two recent studies performed again in the U.S. with the ActHIB vaccine gave a similar range of variation with a post-dose 3 GMT, ranging from 4.4

micrograms to 10.8 micrograms per mL.

We know that there are variations in the anti-PRP immune responses with all Haemophilus b conjugate vaccines. As I just showed you, we have variations for the post-dose 3 anti-PRP GMTs with the PRP vaccine, 2.6 up to 10.8. We have also such variations with other Haemophilus b conjugate vaccines. For example, HbOC vaccine is able to provide levels ranging from 2.4 up to 13.7 and the PRP-OMP vaccine, given with two doses for the primary immunization is able to provide levels ranging from 1.4 up to 6.0 micrograms.

As you know, all epidemiological evidence suggests that Haemophilus b disease has been controlled in the U.S. by the use of these Haemophilus b conjugate vaccines. To illustrate the variations of responses, which can be observed with the HbOC vaccine, you have here the results of four studies performed in the U.S., with the HbOC vaccine where you can see that post-dose 3 GMTs range from 2.4 up to 13 with the corresponding variations of the short and long term protective levels, the long term protective level ranging from 71 up to 94.

For the PRP-OMP vaccine at post-dose 2, GMTs ranges from 1.4 up to 6.0 and the long term protective

level ranges from 60 percent up to 92.

To conclude about the variations of the anti-PRP immune response with the Haemophilus b conjugate vaccines, we know that the level of anti-PRP post-dose 3 are variable and depends on vaccines used, vaccine lots, trials, assays and populations and we consider that the immune response to PRP after three doses of TriHIBit are consistent with historical data from all Haemophilus b conjugate vaccines licensed in the U.S.

The immune response to the pertussis antigens were also evaluated during this study and you have the results from the first evaluation from all groups, the separate vaccine groups and the three combination groups. No difference between the three combined groups were observed for PT and FHA immune responses and the combined lot gave higher immune responses to FHA compared to the corresponding separate vaccines given at separate sites.

In order to compare this data to historical values, we have retested some selected sera. These sera were retested using a revalidated assay as I just mentioned, you, Dr. Frasch, and this revalidation was done in collaboration with CBER laboratory. And these sera were tested in parallel at the same time with all the retention

sera still available at Pasteur Merieux Connaught, coming from abridging immunogenicity study, which was performed in order to generate immune responses against Tripedia by using one of the Tripedia lots, which was used in the German efficacy study, which supported the licensure of Tripedia in the U.S.

And, in fact, we observed very good immune responses against PT and FHA for the TriHIBit group and, in fact, these responses were again higher for anti-FHA compared to both vaccines given at separate sites. When these levels are compared to the levels observed during the bridging study, the immune responses were very high.

The immune responses were also evaluated. The immune response against diphtheria was higher in the combined group compared to the separate vaccine group and within the three combination lots used, one lot gave a lower immune response compared to the two others. This level of immune response was similar to the level obtained in the separate group.

When the percentages of infants reaching a level of 0.01 units per mL, nearly 100 percent of infants reached this level. Regarding tetanus, both vaccines given at separate sites gave higher response compared to the

respective combination group. No differences were observed within the three combination groups and all infants whatever the group reached the level of 0.01 equivalent of mL.

As in one center of this study, infants received HB and OPV vaccine either at the same time of TriHIBit or one month later. We were able to evaluate the effect of these concomitant vaccinations on the immune responses to TriHIBit antigen and basically no statistically significant difference for anti-PRP, anti-diphtheria, anti-tetanus, anti-PT and anti-FHA post-dose three responses were observed.

So, we were able to check the immune response to the HBs and polio virus antigens and whatever the schedule received, either HB and OPV given at the same time or one month later. Very good immune responses were obtained. You have to note that the immune response to the HBs antigen are after two hepatitis B vaccines given at two and four months of age and these responses are after three OPV given at two, four and six months of age.

The second set of immune response data were generated during the large scale comparative evaluation of safety where were able to from a subset of infants to

generate some data. You have here the responses against the PRP antigen. No difference between the two groups were observed, either for the GMT and also for the percentages of infants reaching both the short term and the long term protective level.

These responses are still within the range of expected immune responses as I presented earlier.

The immune responses against PT and FHA antigen are presented on this slide and, in fact, we did observe a higher level of antibodies against PT after the injection of TriHIBit compared to the separate vaccines. No difference were observed for the FHA antigen.

Regarding diphtheria, again, no difference between both vaccines given at supplied sites compared to the combination vaccine. Nearly all infants reached the level of 0.01 units per mL and for tetanus a similar figure was observed and all infants reached the level of 0.01 equivalent per mL.

Similarly, to the previous trial, as some infants may have received at the same time than TriHIBit HB vaccine or OPV, we were able again to document the immune responses to these antigens. These responses for HBs are after three hepatitis B vaccines given at two and four and six months

of age and after three OPVs and, again, a very good immune responses against the HBs antigen and against the three polio virus types were observed.

As I told you, we have performed some additional analysis in order to provide supportive data regarding the quality of immune response to the PRP antigen. To do that, we have firstly on some selected sera coming from the two studies and coming from the two groups, tested the anti-PRP for the IgG subclasses. The main results were that the IgG subclasses. The main results were that the IgG1 was the predominant IgG subclass as expected and that the IgG1/IgG ratio were not different between the TriHIBit recipients compared to the ActHIB and Tripedia recipients.

We have also performed some assays regarding the evaluation of the bactericidal activities of vaccine-induced sera. This work was done in the laboratory recommended by CBER. We have tested limited number of sera but basically whatever the level of killing activity used to express the results, no difference -- no statistically significant difference were observed between the two groups within the two studies, confirming that it seemed that the quality of the immune response induced by TriHIBit does not seem to be different from the response induced by both

vaccines given at separate sites.

DR. FLEMING: Excuse me. Just to interrupt, you are saying no statistically significant difference, but those numbers are incredibly small.

DR. VIDOR: Yes.

DR. FLEMING: So that even though you are estimating huge differences, you have no power. How do you logically conclude that this is evidence that there is no change?

DR. VIDOR: We refer more to this study because this study involve much more serum and as you know, this assay is relatively difficult to perform, time-consuming and it is difficult to perform such an assay on more sera and we agree that the power of these statistical comparisons are low. It is clear.

DR. FERRIERI: I would like to ask you a question about this data on this slide compared to the data in your other briefing book, where of the 52 patients or enrollees rather, you have 96.1 percent with the TriHIBit, who had bactericidal activity in this slide. In your other slide, you had 37 of 52 or 71 percent of bactericidal activity. I am a bit confused.

DR. VIDOR: Because the first slide you received

was expressing the level of 99 percent killing activity and as we have considered -- as we consider that this level of expression of killing activity over 99 is perhaps too stringent. We are presented on this slide levels of killing activity, which are more commonly used to present this kind of data.

DR. FERRIERI: Thank you.

DR. VIDOR: To conclude on the immunogenicity of the TriHIBit vaccine given at two, four and six months of age, we have shown that TriHIBit is immunogenic in infants and provides immune response against diphtheria, tetanus, pertussis and Haemophilus influenzae type b and we have demonstrated that antibody against PT and FHA are at the same level after three doses of TriHIBit compared to three doses of Tripedia and ActHIB given separately.

The last study allowed us to generate some preliminary information regarding the immune response to a fourth dose of TriHIBit given as a booster on children primed with TriHIBit and we were -- here is described the study design for this study, which was an open descriptive study involving six centers and we were able to collect sera before and four to eight weeks after vaccination.

On this slide are presented the immune response

to PRP, which were observed pre and post-booster. The pre-booster level was 0.36 with 73 percent of infants still above the short term protective level and 22 persons of infants still above the long term protective level. The antibody levels after the booster presented a nearly 2 log fold increase with nearly 100 percent of children reaching both protective levels.

To conclude, a strong booster effect of TriHIBit on anti-PRP level was demonstrated in children primed with three doses of TriHIBit. The pre-booster anti-PRP levels were comparable to historical values and the post-booster anti-PRP levels were comparable to those achieved when TriHIBit is given in children primed with Tripedia and ActHIB administered separately.

I will let Jim Williams finish this presentation.

DR. WILLIAMS: Thank you, Emmanuel.

In conclusion, I would like to present a brief summary of the safety and immunogenicity data that was just presented by Dr. Vidor.

Regarding safety, we have a shown a good safety profile for TriHIBit given to more than 4,300 infants. A similar safety profile for TriHIBit compared to ActHIB and Tripedia given at separate sites was also demonstrated.

No clinically relevant variation of reaction rates were observed when TriHIBit was given as a fourth dose in children primed with TriHIBit.

Regarding immunogenicity, the immune response to PRP after three doses of TriHIBit is consistent with historical data from all Haemophilus b conjugate vaccines licensed in the U.S. The biological activities displayed by anti-PRP antibodies induced by TriHIBit are similar to those induced by Tripedia and ActHIB given at separate sites.

Infants immunized with TriHIBit at two, four and six months of age are primed against PRP antigen.

Immune responses against PT and FHA antigens induced by TriHIBit are of the same magnitude or even superior to those induced by Tripedia given alone or in ActHIB given simultaneously at separate sites.

Regarding the criteria for licensure of TriHIBit, we believe that we have satisfied and demonstrated the safety quality of the vaccine. We have also demonstrated the immunogenic potential of the vaccine and we also believe that TriHIBit is an alternative to the use of the DTP whole cell reconstituting ActHIB.

This vaccine is also a step toward a combination

vaccine of a higher number of individual components greater than four.

Thank you very much.

I think we have some time for questions.

DR. FERRIERI: Committee members, this is a good opportunity to ask Dr. Vidor or Dr. Williams or their team members specific questions before Dr. Frasch poses the Agency questions to us. So, anything that you would like to bring up now would be most helpful.

Dr. Edwards.

DR. EDWARDS: Children that responded poorly to the -- or less well to the PRP vaccine, did they respond poorly to other vaccine antigens? What was their immune response in general? Did it appear that they were poorly responsive in general or was it specific for the PRP responses?

DR. WILLIAMS: In providing answers to these questions, I am going to Emmanuel to answer that question.

DR. VIDOR: You are referring to the infants who apparently failed to respond to PRP?

DR. EDWARDS: Yes.

DR. VIDOR: Did they fail also to -- no. Apparently, there was no -- the infants who failed to

respond to the PRP antigen did respond well to the others.

DR. FERRIERI: Yes, Dr. Karzon.

DR. KARZON: Do you have any information about the effect of the product on measles or varicella immunization?

DR. VIDOR: We are in the process to collect data regarding the immune response to MMR and varicella vaccine, given the fourth -- at the same time as the fourth dose of TriHIBit, but we have already got some data when TriHIBit was given at the fourth dose in children primed with whole cell pertussis vaccine.

May I have one back-up slide, which is -- back-up 47, where we have assessed the immune response to the measles, mumps and rubella. This is the immune response to measles, mumps and rubella when TriHIBit is given at the same time that MMR vaccine for a booster dose in children with -- primed with whole cell pertussis. And you have here the pre and post-GMTs and the seroconversion rates, which were very high against measles, mumps and rubella.

DR. KARZON: Do you have a control for that?

DR. VIDOR: No.

DR. FERRIERI: Other points from the table, from the committee?

Dr. Apicella.

DR. APICELLA: Your slide 47, you give a pre-booster dose in the primed children for TriHIBit. Do you have any data on the levels in the children who received separate polysaccharide in the pertussis, diphtheria, tetanus levels at that same period of time? Are they comparable?

DR. VIDOR: These levels which were observed at pre-booster are similar to historical values we can observe.

DR. APICELLA: What about the children that you had in the study, the same study?

DR. VIDOR: We do not have the, during the primary phase of this study, any sera recollected.

DR. FERRIERI: This is a terribly important question. What is your capability of providing an answer for that question?

DR. HOSBACH: Phil Hosbach(?).

As far as collection of that information, it is ongoing. We took the trials, No. 468-08. It is now in the booster phase and we are collecting that data currently.

DR. FERRIERI: Other points? Don't hesitate or if you are a new member of the committee, please feel free

to join in.

Dr. Glode.

DR. GLODE: Could I just ask you a quick safety question? I assume that in these several thousand question there were no seizures within 72 hours. Is that right? Convulsions?

DR. VIDOR: We have had two vaccine-related seizures. We have a back-up Slide 10. Yes, during the compilation of all the serious adverse events, we observed during the studies where TriHIBit or both vaccines were given at two, four and six months of age, and two vaccine-related seizures occurred during these three studies within the TriHIBit group. Any hypotonic-hyporesponsive episodes; 25 persistent cry in the TriHIBit group versus 10 TriHIBit ActHIB and six high fever compared to them.

The two seizures were possibly vaccine related.

DR. FERRIERI: A different question, Dr. Vidor.

Can you or one of your colleagues tell me which Haemophilus influenzae b strain was used in your assay to assess the bactericidal functional activity in these sera?

DR. VIDOR: We ask someone from our laboratory.

DR. FERRIERI: It wasn't in any of the briefing information as far as I can tell.

DR. VIDOR: I think we do not have the answer.

DR. FERRIERI: Is someone -- yes, please introduce yourself and use the microphone.

DR. PETRICAH: Pat Petricah(?).

It is the vaccine strain that we are using.

DR. FERRIERI: Other questions?

Yes, Dr. Fleming.

DR. FLEMING: First a safety question.

In the OA trial, you had noted reduced reactogenicity as you went from two, four to six month dosing. But there were also 8.4 percent dropouts between the two and the six month. Could that have accounted for a substantial amount of that reduction? Have you looked at --

DR. VIDOR: The main reasons for dropouts were withdrawals, loss to follow-up and exclusion by the investigators due to calculations(?).

DR. FLEMING: So, did you analyze the 1,789 at six months to see what their reactogenicity was at two months just to see whether that pattern persisted?

DR. VIDOR: No, we did not do this analysis.

DR. FLEMING: Second question.

If we look at immunogenicity, we have two sources

of direct comparisons. One is from the 01 trial where we have 75 on combination and 69 on separate and you noted post-dose three. If we are looking at percents that achieve the target response of at least 1, level of 1 microgram per milliliter, the combination is 85.3 percent, separate a hundred percent or in raw numbers that means that 11 people on the combination of 75 did not achieve or as all 69 did on the separate, which was -- you had noted significant at the 01 level. By my calculator here on a chi square, it is actually at the 00 -- less than the 001 level.

Then the other source of information is from the 08 trial, where the estimates are more comparable, 74.4 percent versus 77.8 percent or 122 of 164 on combination achieved the level and 42 of 54 on separate achieved the level.

Just doing an informal meta-analysis, putting these two sets of data together, each of which seem to be inconsistent -- in the one case there is a difference at the 001 level and in the second in the 01 trial -- in the 08 trial, there is evidence of no difference. If you do a quick meta-analysis of the two, you will end up with 90 percent in the separate vaccination group achieving desired

level of immune response versus 77.8 percent.

That pool data is still significant at nearly the 001 level. Your thoughts about this, your thoughts about why the results from the 01 study and the 08 study seem to be quite inconsistent and then the pooled analysis shows a noticeably significant difference in the percent of patients that achieve a level of 1.

DR. VIDOR: As I showed you there are variations amongst the reason -- the table compiling the results coming from U.S. studies, which supported the licensure of PRPT showed large range of variation for post-dose three PRP immune risk concern with a ratio of almost 3 between the lowest GMT values to the highest.

Perhaps --

DR. SICS: Howard Sics(?).

Just like to enforce a point that I think was made in the presentation. In presenting the historical data, clinical data that we produced with ActHIB, both in combination and without, the result that sticks out in all of that is the hundred percent from that separate trial.

We have seen high 90s often. That is the only time that we have ever seen a hundred percent. I think it is within in the high range but it somewhat was of more

concern to us than the 85. The 85 was an expected result. The hundred was not.

DR. FLEMING: But even if we acknowledge that by pooling the data in the two, i.e., in the second study, in the 08 study, the estimates were 78 percent -- by pooling the two, we get a pooled estimate in the separate of 90 percent, which from what you are saying is believable.

DR. SICS: Yes.

DR. FLEMING: Whereas, the pooled result for the combination is 77.8 percent. So, we more than double the number of people that don't achieve this desired level of 1. That difference is significant at between the 01 and 001 level. So, it is not just a random event.

Can you explain -- and yet your conclusion is --

DR. SICS: I am not sure how you are doing a random analysis when you carry the aberrant result into the pool. I mean, the second result was a completely new trial at new sites and showed there to be no difference between the separate and the combined. And we believe that to be a more significant result than combining the two.

DR. FLEMING: What you are referring to as an aberrant result is still from a validly comparative trial and even if, in fact, you would have expected less than a

hundred percent, the differences were highly significant. So, it is difficult to conclude that we can ignore that result simply because you had a hundred percent.

When you are pooling all of the data, you end up with 90 percent, which is a very believable result. And we haven't even begun to talk about the fact that in all of these studies, the relevant test isn't of a quality -- a non-significant P value doesn't mean you have established equivalence here. What we are really getting at is do you have an equivalent immune response, meaning that what can you rule out, what differences can you rule out?

And unfortunately, even in this primary analysis, looking at a quality, we are actually ruling out a quality, which is in the wrong direction of what we are trying to do.

DR. SICS: Would you interpret the first trial as showing suppression of the combination vaccine, based on the historical data in the second trial? That is the question, as I understand it. Is there suppression when you mix the two vaccines?

DR. FLEMING: Indeed, and the question is do we-- how important is it to achieve a level of 1. So, turning the question back, if it is important to achieve a level of

1, how much reduction in the likelihood of achieving that level are we willing to accept and still call this equivalent? That is the fundamental question.

DR. SICS: I agree. And that is the reason we presented the four slides, where we compare it to the licensed product in showing the variation that is seen with the three licensed Hib products, and the fourth slide was of the current combination, which is used -- Hib titer that is used in combination with whole cell.

The point that we were making is if you look at the range of PRP responses generated with this combination, it is higher than those or in the high range.

DR. FLEMING: Just to summarize, you are estimating -- in the two comparative studies, you are estimating a reduction of about 12 percent in the number of people who will achieve a level of 1, meaning that although you haven't presented this calculation, that reduction could be as much as 15, 18 percent. So, instead of having 90 percent achieve the desired level of 1, it could be 70 to 78 percent. That is the concern that I wanted to present.

DR. SICS: I think that you have to expect that there is a range of responses that will occur and I think

the data we have presented says that the range to be expected with Hib titer is equal to or better than the combinations that are currently used or the monovalent ActHIB titer combinations of conjugate vaccines.

DR. HOSBACH: This is Phil Hosbach. I would just like to add one comment. I thought your -- it was interesting that you pooled the data in a meta-analysis format, but if you take a look at the numbers from each of the studies, it biases because only 54 were in the separate group in the second study; whereas, there were 200 plus in the combined group when that study was showing virtual equivalence. Had you upped the numbers in each of those groups, you might see less of a difference when doing a meta-analysis in the future.

DR. FERRIERI: Tom, do you have a rejoinder or can we revisit this issue during our formal committee discussion?

DR. FLEMING: Let's revisit it.

DR. FERRIERI: All right. Good. It will permit people to have a better perspective.

Dr. Apicella.

DR. APICELLA: Do you have any data on the change in titer after the fourth dose, compared to children who

get the doses separately? If you don't, do you plan to do this?

DR. VIDOR: Regarding which antigen?

DR. APICELLA: The PRP.

DR. VIDOR: I have presented you with the fourth dose immunogenicity data on PRP.

DR. APICELLA: I am interested in what happens after the dose to the comparative titers.

DR. VIDOR: You mean long term --

DR. APICELLA: Yes, right. Over six months or a year.

DR. VIDOR: Not yet.

DR. FERRIERI: Dr. Glode.

DR. GLODE: In 468-08 amendment to are there then in that study multiple lots of both Tripedia and ActHIB involved?

DR. VIDOR: Yes.

DR. GLODE: Okay. And then if we go back to -- I am just having a little trouble with interpretation, based on the study design of 468-01. So, you might be able to help me with that. So, as I understand it then, there were three different lots of Tripedia and three different lots of ActHIB.

DR. VIDOR: Yes.

DR. GLODE: Okay. And if there had been no differences observed, then -- and the number is large enough, then I guess we could have concluded that you established consistency. Since significant differences were observed, then I guess I have a problem with whether you have established consistency of lots. And I am interested scientifically in whether the Tripedia influences the inconsistency or the ActHIB lot.

Did you have any data that you didn't show us where you hold the lot of ActHIB steady, but you reconstitute with three different lots of Tripedia or vice-versa?

DR. VIDOR: We do not have this kind of --

DR. GLODE: Don't have that.

DR. MISCHEVITZ: Carleton Mischevitz(?).

If I think I understood your question, it was related to the consistency of the immune response for TriHIBit and I think we showed consistency of response for the three TriHIBit lots. It was the separate injections where the question is being raised about a difference between response.

So, I think we have shown consistency among

manufacturing of the three lots. It is the separate versus combined.

DR. GLODE: Well, actually, 525 for the anti-PRP values of the three different combinations, there were significant differences.

DR. VIDOR: Our basic assumptions to demonstrate consistency was made on the percentages of infants reaching the protective levels. When you see the results on the percentages, there was no difference for the percentages of infants reaching both short term and long term protective levels.

DR. FERRIERI: Thank you.

I would like Dr. Frasch to present the questions. The agenda will be he will present the questions. We will then take a coffee break and when we return, we will first have the presentation by Dr. Scheinfeld that was not able to be presented in the official open public hearing earlier.

Dr. Frasch.

Agenda Item: Presentation of Questions

DR. FRASCH: We have four questions. The first question will relate to safety and the next three questions will relate to the immune response data that we have heard.

I will wait for the -- another moment and see if the slide appears.

[Pause.]

The committee will be asked to give their opinion on each of the four questions.

While they are changing the slide, let me just simply state the questions.

The first question, as I said, involves safety and that is: Have sufficient data been presented to show that when Tripedia is used to reconstitute ActHIB that the rates of local and systemic reactions are comparable to when the two vaccines are administered separately?

The second question is: Are the data for the immune response to the tetanus and diphtheria toxoids sufficient to show that the immune responses are comparable following separate versus combined administration of the vaccines?

The third question is: Are the data for the immune response to the two acellular pertussis components, that is, pertussis toxin or PT and filamentous hemagglutinins or FHA, sufficient to show that the immune responses are comparable following separate versus combined administration of the vaccines?

Now, here we have the last one that seems to have caused some of the most discussion and that is: Are the data for the immune response to the Haemophilus polysaccharide sufficient to conclude that the immune response to PRPT is not compromised by combination with Tripedia?

You will note that the question is stated slightly differently than the previous two immunological questions.

That is all the questions. Are there any comments on the questions?

[There was no response.]

Okay.

DR. FERRIERI: Thank you, Carl.

It is time for us to take a break, but we must be back promptly by five minutes to 11:00.

[Brief recess.]

DR. FERRIERI: We will reconvene now, if you could all take your seats. I hope you had a good stretch and feel alive and well.

We will move on to the part of the open public hearing that was not able to be covered this morning. We

have with us Dr. Henry Scheinfeld, who is the co-director of Kaiser-Permanente's Pediatric Vaccine Study Center. He will be presenting some data from the European Society for Infectious Diseases on Combined Vaccines and Demonstrated Interference.

I may not have the title quite correct.

Dr. Scheinfeld, what can we do to help you? You will use the microphone, please.

DR. SCHEINFELD: All I need are a few overheads and I won't take much of your time.

DR. FERRIERI: Thank you.

DR. SCHEINFELD: I thought this would be of interest to this group from the standpoint that many of you have unfortunately not been able to attend the meeting in Paris. I unfortunately had to attend that meeting.

It was of interest, even though the vaccines were European vaccines, but they were related to aspects of interference and as a result, I thought I would just show you the two studies that were relevant to those factors.

The first one was from England and there were 272 infants involved in this study and a subset was studied at 13 and 14 months of age. The routine in England is to immunize infants at two and three and four months of age.

They only -- with Hib, and they do not give a booster dose. They were concerned because of this data relative to where they might go, following these observations.

These infants received PRPT vaccine combined with diphtheria, tetanus, DTaP at two to three, four months of age, followed by a booster dose at 13 months of age. Now, what was interesting was that the pre-levels and the post-levels at five months of age looked entirely the same. At 13 months of age, again, after the three doses, there wasn't very much difference and at 14 months of age, there was considerable priming.

So, that phenomenon of interference at least was demonstrated in those observations. The acellular pertussis was a product that contained 25 mics of PT and 25 of filamentous hemagglutinin. And it was a European formulation for the rest of the product. So, it was, as I found out, considerably different than the United States product of Tripedia.

The second study was a study from Brussels and here there was the priming of -- again, an attempt to demonstrate the priming effect of the combined DTaP ActHIB combination, the Merieux Connaught product in Europe. And, again, here in the pre-immunization level is compared with

the post immunization level of the DTaP and ActHIB separately versus that given in combination.

What one can see here quite clearly is that there is some interference with the Hib titer when the vaccine is given in combination, a significant level at 1 microgram. And I didn't have the data to calculate that at the GMT, but it looked significant there.

They were looking for a priming effect as well and, indeed, they found it, but interestingly enough, again, the pre-booster levels, again, at 12 to 14 months of age demonstrated a significant difference in the level of 1 microgram of antibody in the group that got the combination versus that given separately.

So, these demonstrated aspects of interference, which were of interest and certainly of concern to those individuals working with this vaccine in Europe. That is--

DR. FLEMING: Excuse us. I apologize. Just to make sure this is understood -- that I understand, the doses at three, four, five months or the pre-12 month doses are administered in combination with DTaP, but the booster is active alone?

DR. SCHEINFELD: No.

DR. FLEMING: Or is the booster in combination?

DR. SCHEINFELD: The study demonstrates two groups of children. In this group they got the DTaP and ActHIB separately. They got it combined in the second group.

DR. FERRIERI: Dr. Fleming's question also is that they received the Haemophilus vaccine alone and then the post-booster reflects that, as I understand the data, Tom --

DR. SCHEINFELD: That is right.

DR. FERRIERI: That was all the priming that was done in the left part of the slide with the separate injections and then on the right hand side, the combination.

DR. SCHEINFELD: Exactly.

DR. GREENBERG: Can you move the slide up? We can't see a lot. Just move it higher on the screen up.

DR. FERRIERI: Thanks, Dr. Scheinfeld.

This is the first time that I have seen this data as well and it is really good that you came and did this, Dr. Scheinfeld. It is extremely interesting.

Does anyone want to see his previous slide or you have digested the data? Would you like to see -- would you mind, Dr. Scheinfeld, putting up the previous one? I think

it is the most -- yes, that is the one. Can you move it up just a bit, please? Yes, very good.

So, again, for those of you who may not see it well in the back of the room, we have the post-dose three on the left hand side with the separate injections with 91.8 percent having greater than 1 microgram versus those--68.5 for those who received it in combination with the reconstitution approach.

DR. KARZON: Would you clarify the difference between these two slides then, just summate that?

DR. SCHEINFELD: One represents the booster effect given at 12 to 14 months. This is the dose -- these are the values given after the first three doses, one month after the first three doses. Okay? They were then followed. Blood was drawn again before the booster dose was given and then the booster dose was given.

DR. FERRIERI: Any other question for Dr. Scheinfeld?

Dr. Sics, do you have something you wish to say?

DR. SICS: Yes. First of all, Pasteur Merieux Connaught, France is developing its own set of combination vaccines with its own pertussis antigens, its own diphtheria toxoid, its own tetanus toxoid. It has a

different formulation. The alum is different. The immunizing schedule is different.

None of these studies were done with the vaccine under consideration this morning. They are very different, very different vaccines. I don't know -- is it Dr. Scheinfeld? -- I don't know you. Would you mind telling us your affiliation and what you do?

DR. SCHEINFELD: Sure. I am co-director of the Vaccine Study Center at Kaiser Permanente in Northern California.

DR. SICS: And are you currently doing any clinical trials for a vaccine manufacturer?

DR. SCHEINFELD: Oh, for about three or four of them, sir, yes, I am.

DR. SICS: Thank you.

DR. FERRIERI: Dr. Edwards.

DR. SICS: Would you like to mention them? I think that would go into the file.

DR. SCHEINFELD: Sure. I am doing studies for Wyeth-Lederle. We have done them for Chiron. We are doing them for SmithKline Beecham and we are doing them for Merck.

DR. SICS: Thank you very much. I think that is

helpful.

DR. FERRIERI: Dr. Edwards.

DR. EDWARDS: Could you just put up the first U.K. study again? I am sorry.

I think it is intriguing the pre-titers in the children from the U.K. are really quite high. I don't know quite what to make of that, but, in general, U.S. kids have titers that are generally .05 or something of that nature. And I don't know that it -- but it is interesting that the pre-titers at two months are high. Then is this just two doses, Henry?

DR. SCHEINFELD: Three doses, two, three and four months of age.

DR. EDWARDS: So, the five month data is after three doses.

DR. SCHEINFELD: We looked at these -- I thought we looked at these --

DR. EDWARDS: Right. I just wanted to make sure that was -- but it is interesting that the two month pre-titer is really pretty high.

DR. SCHEINFELD: Quite high.

DR. EDWARDS: Yes.

DR. FERRIERI: Well, to put this into

perspective, I think, it is the concept that is of great interest to probably everyone here in the room, the concept that you may have suppression of immune response, depending on the nature of vaccines that are given together. So, this has great relevance to our discussion today and we thank you.

Agenda Item: Committee Discussion

We will move on then to the focused discussion on the four questions posed by Dr. Frasch and FDA CBER. We have them in front of us, but it might be helpful for the audience if we -- Carl, is it possible for us to put Slide 1 that has questions 1 and 2? Otherwise, I will just read it again.

Have sufficient data been presented to show that when Tripedia is used to reconstitute ActHIB the rates of local and systemic reactions are comparable to when the two vaccines are administered separately?

What we have usually done for anyone new here at the table is a spontaneous response to the question and then FDA is interested in a formal response. So, we will then go around the table for each question and indicate in the affirmative or negative or whatever the appropriate response is to the question.

Who would like to open the discussion?

Mimi Glode.

DR. GLODE: I would just like to ask one more clarifying question from either the sponsor or the FDA.

I have assumed that when very serious adverse reactions, such as seizures, deaths or hospitalizations, were not shown to us that they either -- actually, I assumed that they did not occur, which is, obviously, incorrect. So, I guess I just need to be reassured that there was no difference between the groups and there was no unusual causes of hospitalizations or unexplained deaths or something like that that we were just not shown that information.

DR. FERRIERI: Sponsors, please -- Dr. Vidor.

DR. VIDOR: Regarding hospitalizations, we have a slide to you the rates of hospitalizations, which were observed during the trials. It is Slide 11, which shows, obviously, that we collected hospitalization during these trials. Any of the hospitalizations, which occurred during the trials were vaccine-related and you have here the rates of hospitalization between the two groups, which were similar.

DR. GLODE: And are discharge diagnosis, causes

for hospitalizations also similar?

DR. VIDOR: We have back-up Slide No. 5, where are listed here for one trial the reasons for the hospitalizations and, as you can see, the reasons were classical and no difference in the rates --

DR. FERRIERI: What were the causes of meningitis, Dr. Vidor, in that left column for the TriHIBit group? Do you know if there were bacterial isolates identified?

DR. VIDOR: No bacterial isolates. Viral meningitis.

DR. FERRIERI: You think it was viral meningitis.

Dr. Apicella, did you have a question?

At the projector, please -- it is sharp here, Mike. I am sorry that we didn't appreciate that.

DR. GREENBERG: What is the second one down after bronchiolitis? I can't -- this is like an eye test.

DR. FERRIERI: What is your question -- your question is what is GITD?

DR. GREENBERG: I can't read -- that is --

DR. VIDOR: This? Gastrointestional tract disorder.

DR. GREENBERG: What is the next one?

DR. VIDOR: Urinary tract infection.

[Multiple discussions.]

DR. VIDOR: The denominators were approximately 8 -- 6,000 injections and 2,700 injections.

PARTICIPANT: Were there any deaths in the two groups?

DR. VIDOR: Any death.

PARTICIPANT: No deaths.

DR. FERRIERI: Thank you.

DR. FLEMING: So, this is just somewhat crude guesstimates here, but you are looking at a rate of approximately four times as many hospitalizations, but that is occurring in, from what you just said, about twice as many injections. Is that correct? You said 6,000 versus 2,600.

DR. VIDOR: Yes, of course.

DR. FLEMING: Excuse me. Three -- it is a 3 to 1 randomization.

DR. VIDOR: Yes.

DR. FERRIERI: Please.

DR. BREIMAN: Could I ask does the question also address the issue of booster doses in terms of safety? Is that something you also want to discuss? The data that was

presented, I think, on Slide 18, has such very small numbers -- I think they were 234 observations -- that if one was worried about the more serious types of concerns that have driven the development of acellular pertussis vaccines to begin with, obviously, you wouldn't have the capacity to look at that.

DR. VIDOR: The safety profile of the fourth dose of TriHIBit has already been described previously and three studies have documented these safety profile on approximately 2,500 children and we have already submitted to FDA this kind of data and the product is licensed for the fourth dose.

DR. FERRIERI: Does the FDA have any further response to Dr. Glode's question then? Do you have anything different to say than what we have just heard?

The microphone, please. We are talking about any safety data. Anything that you wish to add?

DR. FRASCH: I am not sure what the question is. Are we talking about -- does Question 1 relate to only the primary immunization series or also to the fourth dose? If that is the question, the application is for the primary immunization series to allow use in a two month old.

We looked at the ability to use it as a booster

immunization for the previous licensure, which occurred in approximately September 1996.

It is true that the fourth dose data at that time was mostly following or almost entirely following whole cell vaccine, but the primary thing on the table today is the primary immunization series, two, four and six months.

DR. FERRIERI: Thank you, Carl.

So, in response to Question 1, is there any other discussion on it from the members of the committee? Do you feel prepared to address the issue of "yes" or "no" on it then? We will start with Dr. Poland.

Are the data sufficient?

DR. POLAND: I vote "yes."

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes.

PARTICIPANT: Yes.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: Yes.

DR. FERRIERI: Mrs. Cole.

MS. COLE: I agree, yes.

DR. FERRIERI: Dr. Villalta.

DR. VILLALTA: Yes.

DR. FLEMING: I believe the data are sufficient

relative to the more frequently occurring types of reactions; i.e., those on the order of one in a hundred or less. The data are sufficient on that basis. For the rarer outcomes, the ones that are more on the .1 percent level, fever above 40, HHE, seizures and the hospitalization issue, there are -- in small numbers, there is no HHE, but there are the two seizures and I think slight excess in fever above 40.

Hospitalizations, I couldn't tell. There is fourfold as many, but from two to three times as many doses were delivered. So, there are slight trends for a slight increase there. So, in summary, I would say the frequently occurring types of adverse reactions, there is sufficient data to establish comparability. For those rarer events, we would need, as we typically do in vaccine settings, we would need postmarketing to be able to nail down whether those more rare events are, in fact, meaningfully increased.

DR. FERRIERI: Thank you.

Dr. Glode.

DR. GLODE: Yes.

DR. FERRIERI: Dr. Karzon.

DR. KARZON: I vote "yes," with an interesting

question of the major difference between the two columns is bronchiolitis and off hand, I accept that as a temporal phenomenon of the winter, that we happened to have an epidemic then, and I know of no prior information, which would make me worry about that particular syndrome. But there it is. There is surely a significant difference between those numbers. But I vote "yes."

DR. FERRIERI: Thanks.

Dr. Hewlett.

DR. HEWLETT: Yes.

DR. FERRIERI: Dr. Eickhoff.

DR. EICKHOFF: Yes.

DR. FERRIERI: Thank you.

And for the record, I also vote "yes" and would like to reemphasize the issue of the postmarketing surveillance that was stated by Dr. Fleming.

We will move on then to Question 2, which is on the screen. Are the data for the immune response to the tetanus and diphtheria toxoids sufficient to show the immune responses are comparable following separate versus combined administration of the vaccines?

First, any further discussion of the question, any information anyone wants to lay out on the table to

tease apart before we would do any official formal voting?

Yes, Dr. Fleming.

DR. FLEMING: It might be relevant to just put forward a concept here that in particular is one that I would like to address in Question 4, but it does, in fact, relate to Questions 2, 3 and 4, and that is, in essence, what is the nature of data or strength of evidence we need to see to establish issues of equivalence. Here what we are looking at in Questions 2, 3 and 4 is the issue, is the immune response relative to various of these measures equivalent when you deliver a combination versus separate.

One important clarification is that equivalence is not established by non-significant P values from tests of equality; i.e., looking at two rates of immune responses and finding that the P value for the difference is non-significant doesn't establish equivalence. It just means the data don't rule out equality.

To establish equivalence on any of these measures, we need to first define what the measure is; that is, the clinically relevant measure, and then we need to define what the smallest difference is of clinical relevance that we would want to be able to rule out; i.e., equivalence occurs or can be achieved when you can rule out

all differences of clinical relevance, which ideally should be defined before we collect the data.

Once that is defined, then, in essence, what we do is we obtain confidence intervals for the relative effects and if the lower limit of that confidence interval rules out differences of clinical relevance, then we have established equivalence.

DR. FERRIERI: Thank you, Tom. That is a critical question and we will revisit that, obviously, when we get to Question 4 that has been the most difficult to struggle with and the most controversial.

Mimi, Dr. Glode.

DR. GLODE: If I could refer the committee to Slide 35 and Slide 41, in the red book here. So, if on Slide 35 -- again, I would just like to clarify if I am interpreting this table correctly because possibly I am not -- but on Slide 35, I guess I would conclude -- now, I do want to separate statistical significance from clinical significance. But I guess I would interpret this then that the tetanus antitoxin GMT was statistically significantly lower in the combined group than in the separate group for the same lot that was studied.

Now, I personally think that has no clinical

significance, but it does address the issue of were they comparable and the answer is that, according to this table, there was a reduction in the tetanus antibody geometric mean titer in the combined as compared to the separate. Am I interpreting that the way everyone else is?

DR. FERRIERI: The sponsors will have to address that, assuming that the double dagger, indeed, does go with the point that you are referring to, 0.14 for the separate versus 0.11 equivalence per milliliter. Is that what you are referring to?

DR. GLODE: Yes. Yes.

DR. FERRIERI: Can you confirm that, Dr. Sics, that that is correct?

DR. SICS: I would like to refer you a little bit lower in the table.

DR. GLODE: Okay.

DR. SICS: The reason that 0.01 was chosen to show responses is that is the protective correlate for humans. So, we believe the meaningful data there are how many people reach a protective immune response, not necessarily what the geometric mean titer is.

In direct response to your question, there is a statistical difference between the GMT. We think that it

is clinically irrelevant because 98 percent of the people or better all get a protective immune response. To confirm that, there is an animal model that one can use to challenge and we have actually taken some of the low level sera and challenged in those models to make sure that they were getting a protective response and they were, in fact. I don't know if we -- we have a slide if you would like to see the data that we could show.

DR. GLODE: No. And I have no disagreement with the fact that it is likely to be clinically insignificant. I am just interested in the scientific issue of is there some suppression of the tetanus antibody response in combined versus separate?

DR. SICS: We don't believe that is real suppression. We believe there is some variability between the group, but if you look in the other group, we saw some idea that the diphtherias were enhanced. I am not sure either one of those are real differences in responses or variability that one sees in doing clinical trials.

DR. FERRIERI: Thank you.

The other table you wished to refer to, Dr. Glode, is 41?

DR. GLODE: Well, it was just another chance, I

guess, to look at the same issue. Again, now, perhaps not quite as pure data because all the lots are -- various different lots are used, but I guess I am just assuming there that was no statistically significant difference between the geometric mean titer. Nothing is stated. Is that a correct assumption?

DR. VIDOR: Correct.

DR. HOSBACH: One comment. This is Phil Hosbach.

In that study 468-08, it was a single lot used in both groups. 468-02 is the one with multiple lots.

DR. FERRIERI: Thank you.

Other points about the data presented relative to Question 2 on tetanus and diphtheria toxoid antibody responses?

Yes, Dr. Greenberg.

DR. GREENBERG: Can somebody help me?

Does this mean that with .01 being the biologically relevant level, does that mean that all these levels are tenfold above -- is that what you are saying, that you have ten times as much antibody as you would possibly need to be protected? Or am I misinterpreting that?

DR. FERRIERI: That would be my interpretation.

Sponsors are nodding their heads "yes," Dr. Greenberg.

Dr. Frasch, do you have anything to add to that point?

DR. FRASCH: No.

DR. FERRIERI: Thank you.

Other questions regarding the data we have seen then?

Dr. Fleming.

DR. FLEMING: I think the discussion on Table 35 does help to further enlighten this issue of statistical significance and clinical significance achieving statistical significance on a measure that is not clinically significant isn't significant.

DR. FERRIERI: Thank you. That is one of the best statements I have ever heard a statistician make.

DR. FLEMING: And helpful.

So, it would seem advisable that the first step is to really carefully define what is clinically significant and define what differences in those clinically significant measures are clinically meaningful and then apply statistics to that to determine whether or not we can achieve substantial evidence or significant evidence relative to that particular measure.

So, in the case of Table 35, what we were seeing was for the tetanus GMT, we were seeing a statistically significant difference, but that is not really clinically significant. As was pointed out, you have defined what is clinically significant here is to be able to achieve with high reliability, levels of .01, which is what I am interpreting to be your judgment of protective measure.

So, having stated that, then what the key question is, how much -- if we can achieve a hundred percent with separate administration and we would tolerate slightly less than that with combined, how much less would we tolerate before we would judge that to be clinically meaningful? And, in essence, that is how we establish equivalence. Then just to apply statistics to that to rule out that you would achieve a clinically meaningful reduction in the percent of people that achieve this protective level.

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: I think the other thing that we need to keep in mind is that these children are programmed for two more immunizations.

DR. FERRIERI: Okay.

Dr. Karzon.

DR. KARZON: The .01 level in some ways is very arbitrary. In fact, the reality is that we recommend booster doses every decade for adults, something that we don't do very well in the United States, but epidemiologically we are safe because I suspect that the challenge hasn't been here to really aggressively challenge the decay results.

This was shown in the outbreak in Europe that you all know about where in situations where the challenge is high, that .01 may have been a shaky level for adults. So, the other dimension in the .01 is its longevity and our ability to sustain that level with the subsequent boosters, as Mimi pointed out, or with this every decade further immunizations, which is always going to be a problem to enforce from a public health point of view.

It would also be of interest to me to see what the percentage is at .1 for both diphtheria, where we have more challenge experience, and the tetanus, the challenge is irregular and in small numbers. So, I am not sure we have those numbers with security.

Nevertheless, I am going to vote for this.

DR. FERRIERI: Thank you. I appreciate your moving us in that direction.

Dr. Poland.

DR. POLAND: Just one question. Really probably a request for help from Tom.

With the numbers that we have here related to this particular question, what kind of power do we have to find a relevant difference if one existed? Can you guesstimate, Tom?

DR. FLEMING: That is a very relevant question because what I was coming back to earlier, in order to answer the question positively that we have established equivalence, we have to be able to rule out reductions in percentages that receive this or achieve this protective level that would be clinically meaningful. So, if we are estimating it to be a 1 percent reduction, we need to know the width of that confidence interval. And that is directly a conclusion or a consequence of the sample size.

I don't know if the sponsor has that. I don't have that particular calculation at hand. My sense is that the reduction is that would be possible when we are estimating it to be a hundred and 99 percent is probably not more than a few percent.

DR. FERRIERI: Any comments from Pasteur Merieux Connaught?

Dr. Vidor.

DR. VIDOR: Yes. The study was originally planned to have 80 percent to detect a 15 percent different on the percentages of infants reaching the protective levels. And to achieve that, the number of subjects needed was 76 per group.

DR. FERRIERI: Thank you.

DR. FLEMING: Eighty percent power to detect a 15 percent difference?

DR. VIDOR: Yes. For D and 10 percent for T.

PARTICIPANT: 50 or 15?

DR. FLEMING: 1-5, 15 percent difference. Now, what we are observing is a 1 percent difference in the diphtheria, a hundred versus 99. And in the tetanus it is a hundred versus a hundred. The study is certainly underpowered because a 15 percent difference, I would assume, would be highly clinically meaningful. But without these -- I don't have the exact calculations, but off the top of my head, my belief is we are estimating a hundred versus 99, which is a 1 percent reduction and in the confidence interval probably would not go beyond about 4 or 5 percent difference.

DR. FERRIERI: Thank you.

We will start with Dr. Eickhoff then on the formal response, whether the data are comparable following separate versus combined for tetanus -- immune responses for tetanus and diphtheria toxoid.

DR. EICKHOFF: I will vote yes.

DR. FERRIERI: Dr. Hewlett.

DR. HEWLETT: I think there is another issue here. We are talking about -- the term "variability" in responses has been used on a number of occasions and certainly that does occur. When we see in one study the diphtheria response in the combined vaccine is higher and in another study it is comparable or lower, that may well reflect variability in populations and from studies.

It seems to me -- and I don't want to get ahead of where we are, but it seems to me variability with regard to these other antigens probably is an appropriate term; whereas, the phenomenon of interference or suppressed immune response is one that has been seen repeatedly in different studies with different vaccines.

Dr. Sics referred to a different composition of the vaccine that is being developed in Europe for combination, but it seems to me the data that we just saw suggests that there is, even though we don't necessarily

understand the biological mechanism at the moment, there probably is some phenomenon, which is occurring in combining these vaccines. It is only a matter of degree as to whether it is present or not.

That is different than the variation that we are seeing with the response to the other antigens. But given that, I vote "yes" on the present question.

DR. FERRIERI: Thank you.

Dr. Karzon.

DR. KARZON: I vote "yes."

DR. FERRIERI: Dr. Glode.

DR. GLODE: Yes.

DR. FERRIERI: Dr. Fleming.

DR. FLEMING: On this measure, I accept "yes" because although we don't have the exact figures, it is highly likely that this difference is at most on the order of 3 or 4 or 5 percent.

DR. FERRIERI: Dr. Villalta.

DR. VILLALTA: Yes.

DR. FERRIERI: Mrs. Cole.

MS. COLE: Yes.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: Yes.

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: Yes.

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes.

DR. FERRIERI: Dr. Poland.

DR. POLAND: Yes.

DR. FERRIERI: Thank you. And for the record my vote is "yes" also.

Could we have the slide then for Questions 3 and 4 so that everyone can continue to ponder them?

The next question is similar in many ways, only we are talking about a different organism. Are the immune responses to the two acellular pertussis components, PT and FHA, sufficient to show the immune responses are comparable following separate versus combined administration of the vaccines?

We will first have any spontaneous comments on this point that we haven't already brought up or anyone that wanted to reemphasize them.

Dr. Edwards.

DR. EDWARDS: I think that Slide 34, certainly we have a lot of experience from the NIH trial looking at this particular vaccine in American children and I think that

the 468-01 sera does, in general, have much or significantly higher titers than we have seen in previous studies that the NIH has sponsored. Although in the second part, the 35701, those are, indeed, very comparable, both in the separate and combined to what we had seen earlier in previous studies.

So, I think it, again, confirms that this looks very comparable to other studies, either the combined and the separate and I think is, indeed, quite reassuring.

DR. FERRIERI: Thank you, Kathy.

Other points on this data?

[There was no response.]

All right. Then I think that we should vote on this because the fourth question is going to take considerably more time.

Dr. Poland.

DR. POLAND: I vote "yes."

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes.

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: Yes.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: Yes.

DR. FERRIERI: Mrs. Cole.

MS. COLE: Yes.

DR. FERRIERI: Dr. Villalta.

DR. VILLALTA: Yes.

DR. FERRIERI: Dr. Fleming.

DR. FLEMING: I think the FDA has made this question a lot easier in that we are simply asked to determine whether or not the PT and FHA responses are similar to establish equivalence. I vote "yes" to that, as well, although I think we are making a major assumption that the PT and FHA are valid correlates or surrogates in this setting, but we weren't asked to address that.

DR. FERRIERI: No, we were not, Tom. That is another day.

Dr. Glode.

DR. GLODE: I vote "yes."

DR. FERRIERI: Dr. Karzon.

DR. KARZON: I vote "yes."

DR. FERRIERI: Dr. Hewlett.

DR. HEWLETT: Yes.

DR. FERRIERI: And Dr. Eickhoff.

DR. EICKHOFF: Yes.

DR. FERRIERI: My vote is "yes" also.

Now we will move on to the question that really raises lots of questions, red flags. Are the data for the immune response to the Haemophilus polysaccharide, PRP, sufficient to conclude that the immune response to PRP is not compromised by combination with Tripedia?

I wonder if we could have an opinion, not necessarily an opinion, but just some comments in general on immune responses to this from Dr. Daum, who is sitting on the sidelines. If it could be very brief and without slides, perhaps this could be valuable for the whole audience.

DR. DAUM: Very brief and guaranteed no slides.

I have been following this story for a long time and had a couple of comments that I thought might be helpful to -- at least as discussion points to be considered here. The first one is really that we like to point to Haemophilus as the situation where we have the correlate or the surrogate for protection and we rely a lot on this number 1.0, but I would like to remind everybody how that number came to be.

It really came from a different era. It came from when we were considering immunity rendered by unconjugated capsular polysaccharide. It came at a time

when that was the major provision of host defense offered by a different kind of vaccine. We now live, of course, in the conjugate vaccine era and we cling to this number 1.0 in part because we don't know how else to do it, but we must remember that conjugate vaccines probably work differently and provide more to a host than simply circulating anti-capsular antibody.

I am not trying to downgrade the importance of circulating antibody. It is very important, but they also prime a host for subsequent response to at least unconjugated capsular polysaccharide vaccines -- we know that -- and, hopefully, to the organism if it were presented and they also induce a reduction in asymptomatic carriage, which I believe in the population basis is an important effect in helping the population become immune.

So, we have -- we stick to this 1.0 number and, yet, we must remember that it doesn't necessarily dictate protection. Other things are important as well. There are two instances that come to mind that may be used to reinforce this point. One is one of the trials that was done in Finland, where the geometric mean antibody was well less than 1.0. On the other hand, the efficacy estimate was around 90 percent in that trial. I think that is an

interesting possible reinforcement of that point of view.

During the break, Neil Halsey reminded me of a concern about PRP OMP at one point in time, where there were several lots out there that were much less immunogenic than we all have been led to believe and as best people could do -- Dave Greenberg in Los Angeles and Matu(?) Santocium(?) and their colleagues in the Southwest in the Navajo and Apache, looked for a reduction in efficacy during that time and were unable to demonstrate any.

So, now comes the question to conclude that is how to interpret interference. We look to this 1.0 level and we calculate a percentage of children, who are over it and then look at a combination vaccine and try and compare that percentage and also compare the geometric means by statistical analysis.

This interference issue troubles me. It troubles me because it is seen in virtually all the trials and all the combinations that have been developed. I must say I would be much more comfortable if we understood the mechanism by which it occurred.

But leaving that question aside for just a moment, I think the real question that the committee is going to have to grapple with is how much interference is

okay and how much interference is too much. I think that until that fundamental question is dealt with, it is going to be very hard to interpret the data that we have all seen this morning.

If, for example, separate injections achieve a geometric level of 10 and the combined was 5, is that okay? 4, 3, 2. Where is the cutoff? And I think that that is an issue that I would recommend you deal with right now as best you can because it is going to come up again and again and again if we don't.

So, I thought those comments might be helpful.

DR. FERRIERI: Thanks so much, Bob.

Dr. Fleming, could you pick up on this theme, please?

DR. FLEMING: I completely concur. I think that is nailing the issue of greatest concern to me as well, which is if we are charged with the need to address whether these data establish equivalence, it seems we have to be very clear up front about what clinically we interpret to be equivalent. Or the way I would state that is what reductions in immune response would we allow to occur, what level, before we would then say this is clinically meaningful? We don't want to go beyond that point.

If we choose to use 1 as the level, and maybe we shouldn't be using that, but for the moment if we choose to use 1 as a level and we can achieve, let's say, 90 percent of individuals achieving 1 with separate, then in the combination, are we willing to allow that to drop to 80?

Then I think we are positioned to be able to say do the data allow us to establish equivalence. So, it seems to me that a careful clinical discussion of what we mean clinically by the type of immune response, we need to see to be equivalent is critical to be addressed first.

DR. FERRIERI: Thanks. You are right on target.

Dr. Edwards.

DR. EDWARDS: I think it is important to, again, highlight that the combination that has consistently been shown to interfere with immune responses has been Haemophilus. In general, all the studies have projected that there is not meaningful interference or really significantly statistically significant interference with the pertussis antigens or with other antigens, but time and time again, the interference has been seen with the Hib antibody response.

So that is a source of concern and we certainly do not know the mechanism by which that is caused. I

think, however, it is very important to point out that the variability of the immune response to the Haemophilus vaccines has been a major problem for over a decade; first, because there has been initially with difficulty comparing antibody responses, one vaccine to another, one lab to another and certainly the FDA has been a real leader in making sure that we can compare the immune responses. So, I think we certainly have a good standardized assay.

But even using that standardized assay, I think it is remarkable that you can look at different lots of vaccines that are not combined. And, for instance, some of the studies that we had done that had looked at this particular vaccine had antibody titers that were in the 3, 4 range, actually that are lower than what you are talking about in some of the combined products.

In addition, I think it is important to remember that the Merck vaccine, which is very -- has been very effective, in general, makes antibody responses that are much less than any that we are looking at for this combined product. So, I think that if we are fixated on a number, there are a number of instances that number is significantly lower than what we are seeing in the combined product, are being used and apparently are being effective.

I think, finally, last week I took care of an infant that had Haemophilus meningitis and vaccine failure and I think it is important to remember that we are going to have to be exceedingly careful about, first of all, recording the patients that may, indeed, be failures if we license combined products and giving clinicians a way to actually have these children evaluated in terms of their immune responses, in terms of what vaccine they had received in a way that is really very meticulously done so that we don't lose what we have gained in the past.

Thank you.

DR. FERRIERI: Other comments from the table?

Does anyone feel a need to have a refresher on the data, one slide maybe that would summarize this particular issue? Carl, is there a slide that you would like to have that would best represent what we are struggling with? Or don't you think we can do it in one slide, a slide of the sponsor's?

DR. FRASCH: I think we should like the sponsor choose.

DR. FERRIERI: Okay. Would the sponsors like to show us a slide that exemplifies the issue that we are struggling with, please?

DR. FRASCH: While they are discussing that, I think Dr. Edwards' points were very well-taken.

PARTICIPANT: Carl, how about the two slides we prepared?

DR. FERRIERI: I have those in front of me, from 468-08.

PARTICIPANT: You mean, 468-010A?

DR. FERRIERI: If you would like to show yours, the slides of Dr. Frasch were Slides 3 and 4 in the -- for the committee members.

PARTICIPANT: I think we should look at the data that they put together.

DR. FERRIERI: Fine. Everyone can see these figures then? Is this the slide the sponsors wish to show?

[Multiple discussions.]

That was helpful for us. This is also the slide that Dr. Frasch had presented as Slide 4. This is at post-dose three. The combination had an n of 164, the separate of 54 and you see comparable percentages at the two antibody cutoffs indicated.

Dr. Glode.

DR. GLODE: I would just like to make a comment about the consistency or inconsistency of the degree of

interference as at least for me in an important issue. If we don't know the mechanism and, therefore, we don't know exactly what variables are critical and they could relate to lot differences in either the Tripedia component or they could relate to lot differences in the ActHIB component.

I realize this is using the retrospectroscope, but it would have been extremely helpful to me to go back to Slide 26 and to have seen the data for A plus 1 separate versus A 1 combined; B plus 2 separate versus B 2 combined and C plus 3 separate versus C 3 combined. I know that data doesn't exist, but that would have given me some idea of the consistency of the interference based on different lots of Tripedia and different lots of ActHIB because now I don't know the breadth of that possible interference, which appears to be different in this slide and nonexistent, compared to Slide 26.

And, yet, there was no changes, as I understand it in the manufacturing of the vaccine. So, I must conclude that this is lot-to-lot variability in the interference. Is that correct?

SPONSOR: -- also ranges for vaccine. This is not unusual to this vaccine. If you would please put up Slide 27. And in this slide you can see from various

studies of PRPT given at two, four and six months of age, the far left hand column over here, percent greater than 1, as Dr. Vidor presented earlier, the range of responses here are from 75 up into the mid-90s.

Then if you would show Slide No. 30, please. Now, this is another licensed vaccine, HBOC Hib titer. As you can see here, the GMTs of this licensed product varied from a 2.4 up to 13.7.

Then Slide No. 31, please. This is the PRP OMP vaccine from Merck and, again, you can see ranges of response are greater than 1 microgram of -- here, 60 percent up to levels in the 90s. So, it is not unusual for all of the licensed vaccines to show this kind of variability among manufactured lots.

Yes?

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: This is for Bob Daum.

Bob, is there any information about the relative level of antibody as a function of eradication of the carrier state?

DR. FERRIERI: Please, turn off the slides.

Dr. Daum.

DR. DAUM: I think the easy, simple answer is

"no." I think we don't understand how the eradication mechanism really works. There are many experts on this in the room. I will just offer very quickly my own ideas. I think that conjugate vaccines produce such high levels of IgG that it is likely that this antibody gets into the secretions where the organism likes to attach and thereby blocks carriage. But that is nothing more than speculation and we don't have the information that we need to really answer your question well.

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: It seems to me we know that there is variability in basic vaccination and it seems that there is a reproducible interference. The critical question, which I don't know the answer to is if you took a low level response at the 1 microgram level and added interference on top of that, would you ever drop below the biology that you want? And is there any way that we would know that doesn't happen?

I haven't been given information to figure that out.

DR. FERRIERI: Other comments on this point?

Dr. Sics.

DR. SICS: I think that the comments on the

variability of the response are certainly relevant to the Hib conjugate. I think we shouldn't forget that according to the last publication I saw from CDC, that 98 percent of the Hib b vaccine has disappeared from the United States with the antibody titers that we are showing up there for the licensed products that are being used.

That is a pretty good success story. I also think that we are focusing on one specific comparison in all the data that we have showed you on the Hib responses. You are comparing an 85 percent greater than 1 to a 100 percent greater than 1 and interpreting that as suppression. When you have a variable response, I am not sure that that really means suppression. And we have no other evidence that when you put it in TriHIBit there is a suppression of the PRP response. That is the only single piece of data that suggests there might be. Even in another trial, where we did another randomized population and looked at it, it was not seen.

This combination vaccine is not a liquid product. It is a reconstituted product and it is given immediately after mixing. The problems of formulation are not the same as they are when you make a fully liquid product. All of the trials that I know about where suppression has been

seen significance -- real suppression of PRP responses, they have been liquid products, not with reconstituted products.

DR. FERRIERI: Thank you, Dr. Sics.

Could we refocus the question, though? We are addressing are the data sufficient to conclude that the immune response is not compromised by the combination with Tripedia.

Carl.

DR. FRASCH: One comment. We were also concerned about whether or not there would be variability. So, what we did was since the study was done in four different study sites, we looked at each study site independently; that is, we looked at -- for the moment we said there were four independent studies. The numbers in those sites were about 50 per for the combined and 15 to 20 per for the separate.

We got ranges of seroconversion to 1 microgram of 87 percent, 86 percent, 90 percent and 80 percent. It seemed that one of the study sites was lower consistently than the other three study sites. For what reason, we don't know.

DR. FERRIERI: Are we ready to address the question?

Dr. Eickhoff.

DR. EICKHOFF: As a non-pediatrician in this group, I would like the sponsor to address specifically what is meant by reconstituted vaccines as opposed to liquid product. Does "reconstitution" mean mixed at the time of administration?

DR. SICS: That is correct. What is supplied to the pediatrician is ActHIB, which is a lyophilized product. And Tripedia or right now a whole cell DTP, which is a liquid product that is used to dissolve the lyophilized powder of ActHIB, it is mixed and injected into the patient at that time. It is not stored in a liquid form.

DR. FERRIERI: Thanks, Dr. Sics.

Other points? I think we should move ahead then. We will start down here with Dr. Poland.

DR. FLEMING: Comment.

DR. FERRIERI: Yes, Tom.

DR. FLEMING: I wanted to allow the clinical discussion relative to the issue of what is the proper measure before -- could I have Slide 27 one last time -- before making a statistical interpretation.

DR. FERRIERI: People at the table can turn --

DR. FLEMING: And it is also on your table on

page --

DR. FERRIERI: -- turn to it, please --

DR. FLEMING: On slide, page 27.

PARTICIPANT: While they are bringing up the slide, I would like to make one comment that might have some relevance and it ties in to what Bob Daum mentioned earlier. And that is we previously developed another conjugate vaccine, Prohibid(?), PRPD, which was never licensed for infants in the U.S., but it was licensed for infants in Germany and it was the only vaccine used in Germany during the period of time when Haemophilus disease was reduced dramatically and almost eliminated. That was a vaccine that provided a GMT of somewhere in the range of 0.5 for GMT.

So, I think those kind of factors are important in the consideration as well.

DR. FERRIERI: Tom, would you like to --

DR. FLEMING: Sure. A brief summary.

If we look at that as our attention was called to earlier, the far right hand column, then if we are, in fact, still at least substantially looking at the percent of people that achieve a level 1, we certainly do see in the historical experience some considerable variability in

those estimates in separate, running from 75 to 97 percent. The data in the 01 study and the 08 study are not inconsistent with this type of variability. We are estimating a hundred percent and we are estimating 77.8 percent.

So, in that sense, these two randomized comparative trials are not out of line with the historical experience and in both cases, both in the historical experience and in the randomized trials, if you look in the aggregate, you are getting an estimate of about 90 percent of people with separate administration will achieve a level of 1; 90 percent from the historical experience and 90 percent by averaging the hundred and the 77.8.

If we look at the two randomized trials, what we see -- and as one of my colleagues earlier noted -- and if we do so with proper adjustment for sample sizes, what we see is 90 percent in the two trials versus 80 percent in the two trials, one study showing a difference of about 15 percent and the other one showing a difference of about 3 1/2 percent and those two together were a difference of about 10.

Now, that is the point estimate. The confidence intervals, which we weren't presented, would show

approximately that the level of patients or participants that would achieve this level 1, it is estimated to be 10 percent less and could be at a lower limit of the confidence interval, 15 to 20 percent less. So, we would be looking at 90 percent achieving this level with separate. We are estimating 80 and the lower limit of the confidence interval could allow that to be as low as 70 to 75 percent.

So, that is where statistics takes us on this issue. So, then the question is that we are being asked to address if we address it in terms of achieving a level of 1 is a reduction or is an increase from -- a reduction -- it is a reduction from 90 percent to roughly 70 to 75 percent achieving this level, a difference that is clinically relevant because we can't rule that out with the data.

DR. FERRIERI: I think that is exactly where we are and some of the pediatricians who deal with this issue at the table might want to address that. Is that acceptable or not to you?

DR. EDWARDS: Well, I think that early on Michael Decker(?) and I did a study, which is up there, that compared the four vaccines, PRPD, as well, and there certainly was a difference in the immune response to the

various vaccines, which we showed. But, in general, all of the titers were quite low and we were achieving levels with 1 percent greater than 1 in the 80 percent range. So, I personally am not uncomfortable with the numbers that we are seeing with the combined product, given the variability in studies that I have personally done myself that have, obviously, gone on to -- these vaccines have gone on to be licensed and shown to be highly effective.

DR. FERRIERI: Dr. Glode, how do you react to this?

Could we have the lights up a bit, please?

DR. GLODE: My concerns really just go back to the issue of the range of interference that might be noted. So, what I see is two studies here with two different lots. One shows statistically significant interference by all measurements, which may not -- which, again, we can argue may not be clinically significant and the other one didn't, although it showed lower responses, if you will.

So, my concern relates to whether there has been enough sampling, since we don't know the mechanism, of the range of interference.

DR. FERRIERI: Dr. Breiman.

DR. BREIMAN: One also potential hooker, I think,

in terms of doing the kind of off-the-cuff analysis that Tom just did is that I assume that there can be assay-to-assay variability as well. It is mentioned in the conclusion slide on Slide 32. Do we know how much assay-to-assay variability is expected in -- you know, in one case, we are comparing paired specimens that are run presumably blinded and so forth and making that kind of comparison.

In the other case, we are looking at a number of different tests done in different laboratories or different times and may very well account for substantial variability. So, I don't know what is known about the lab test variability itself.

DR. FERRIERI: Well, there is a tremendous amount that has been done on it. Dr. Frasch, would you or one of your colleagues like to comment on that?

DR. FRASCH: I think most of these assays were done with a standardized radioimmunoassay. I think Dr. Edwards having actually done these assays could comment on that.

DR. EDWARDS: I think you are the guru, Carl.

DR. FRASCH: You have done the assays.

DR. EDWARDS: Well, the company did the assays

here as well, though.

DR. FRASCH: I think his point is -- I mean, Rob's comment is exactly right. When we are trying to look at the historical record, yes, these assays were done at different time intervals, different populations. I think we do have to look at these values in the historical perspective. Otherwise, we would lose what the meaning is also.

DR. FERRIERI: Would you consider that the variability in the assay could be as great as 10 to 15 percent, Carl?

DR. FRASCH: Yes.

DR. FERRIERI: Would that be the best ball park figure we might come up with then under the best circumstances when done meticulously -- I have done a lot of FARS(?) and I would have to conclude that that is probably for other antigens --

DR. FRASCH: Well, we have been doing ELISA assays and we were accepting an intra-laboratory coefficient of variation of plus or minus 20 percent as being quite good.

DR. FERRIERI: So, with that information, what is your reaction, Dr. Breiman?

DR. BREIMAN: I think it is apples and oranges really then. I think the type of comparison that was done in a paired way, you know, in the same laboratory looking at those that -- you know, sera from people that had combined versus individual, separate, I think, is very different. I don't know if you can draw the conclusion that the kind of variability that was seen on that -- you know, on the slide of the multiple studies necessarily reassures you that you are not seeing an important -- potentially important, that not being established yet -- reduction as a result of, you know, a combination approach.

DR. FLEMING: That would mean -- if I interpret what you are saying, you would put particular emphasis on those careful comparisons from randomized assessments that are -- and we have two.

DR. BREIMAN: Yes.

DR. FERRIERI: Other points?

Dr. Hewlett.

DR. HEWLETT: In addition to the issue of biological relevance and whether the decrease is enough to be significant in terms of protection, the other way, I think, that it is useful to look at this is if we acknowledge the fact that the interference phenomenon does

occur, and I think that there are enough studies that demonstrate that, at least one of these studies indicates that this particular product doesn't have that problem and the other studies suggest that it may.

Is that a result of changes in this vaccine relative to the others; that is, that are adequately reproducible? Dr. Sics suggested that there are some differences that they think may be contributing to the fact that there are differences here from the previous studies. Is that phenomenon -- are we satisfied that it is reproducible enough that it will be present in all of the products that are made by this formulation in the future? Do we know enough about it to conclude that?

DR. FERRIERI: Dr. Karzon.

DR. KARZON: This takes into account some things, which assuaged me. One is the history of this number of 1.0. It is arbitrary. We don't know that number. We chose it, I suppose, largely because we could attain it and it worked. It has no other origin base. So that now when we say we want 90 percent at that number of 80 percent, we are dropping down to that now, again, that is arbitrary. We don't know what protects.

And I am willing to accept that because it has no

other landmark which is better upon which we can base this. When I see numbers down in the 80, I -- it bothers me because it isn't that 90 that I think -- that I remember some of us wanted to attain.

The other thing that assuages me is the natural history of the disease. Historically, it has been a disease of young children, not just children, and the antibody was acquired very early. Adult disease was almost a reportable disease in the literature. I think we have a long term project to make certain that this is a controlled disease.

We are also helped by the fact that we can get rid of the organism on the mucosa, which we can't do very easily with some other agents that go on into adult life. I am also bothered by the lack of consistency of the tests, the assays themselves and I wonder if we can't clear this up.

The other variable in the vaccines with different manufacturers now use entirely different starting points, different carriers, for example, which could be very important in this business of drop in titer.

Saying all that, I vote "yes."

DR. FERRIERI: You vote "yes" that the data are

sufficient to conclude that the immune response is not compromised.

Dr. Eickhoff.

DR. EICKHOFF: Are we voting?

DR. FERRIERI: We are voting.

DR. FLEMING: Can I ask for a clarification before we --

DR. FERRIERI: Yes.

DR. FLEMING: Quick clarification. Is the absence of knowledge then justifying the conclusion of equivalence because what I thought, David, you were saying was -- and I understand this -- we can't say we know 1 -- reaching a level of 1 is synonymous with protection. Ideally, we should be looking to see whether or not we see a reduction in protection directly by looking at infection as the endpoint, but we are arguing that we are going to rely on a surrogate instead.

Far be it from me to be an advocate of using surrogates, but if we, in fact, acknowledge that we are not going to do a study to look at the actual endpoint of infection, we are going to use a surrogate, then we are relying on our ability to establish equivalence on that surrogate and if we challenge the relevance of that

surrogate, does that mean that we can readily conclude equivalence?

I am having trouble with that.

DR. KARZON: I have the same trouble but I must tell myself that when I vote with a 90 percent level being satisfactory, that I don't know those answers either.

DR. FLEMING: So, what do we need to see scientifically to be confident about the issue of equivalence?

DR. KARZON: That is tough. You are asking the design of a public health and laboratory follow-up, which might clarify this in the future. One approach, of course, is to look at the products themselves. OMP is a different beast than tetanus as a carrier and what are the implications of that in terms of immunogenicity and survival of the antibody and what are the differences in the possibility of some kind of an interaction with each of them, which is different when another product is added to it? These are questions that I think could be addressed by extensive studies of children, which I visualize as being extraordinarily difficult.

Keeping your ear to the ground on breakthroughs, as Kathy has reported, if one occurs, others can. And it

would be nice to have known what a titer is before, but these kinds of studies are extraordinarily difficult to do.

Then reappearance of the flora, appearance of adult cases, I think surveys of looking for longevity would be a good idea. One of the values of having a higher titer rather than a lower titer clearly is it is going to last longer and that is reassuring. From a public health point of view, it is wiser.

So, I think follow-up of various sorts might be instituted and some work in the laboratory is needed.

DR. FERRIERI: Dr. Edwards.

DR. EDWARDS: I think that perhaps we are all fond of our own data. So, I must acknowledge that, but in our study where we compared the four vaccines, the PRP OMP vaccine, which is supposed to be given as two doses, we actually used a three dose schedule so that we would have it comparable and our percent that achieved greater than 1 after three doses of OMP was 55 and that is a licensed vaccine.

DR. FERRIERI: Dr. Sics, do you have something you wish to say?

DR. SICS: Yes, please.

In regard to the PRP assay, a number of years ago

when people first started working on the Hib conjugates, there was a comparative study done with the manufacturers, CDC and with FDA and also with a central lab, which was used to run a lot of the assays. I mean, the comparison of our assay with the FDA assay and with other assays is in the literature and they were actually not so bad at that time. They were pretty good.

I don't know that we can -- I wouldn't want to say that the variability you are seeing is due to the assays. Part of it may be, but I think it is also partly the conjugate.

The other thing, the point that I was making, I would like to rephrase it in regard to reconstitution versus liquid. I am not suggesting that if everybody goes to reconstitution, they will solve all their problems. I am saying that this is a different vaccine. It has different pertussis components. It has different DNT(?), different formulation than the other vaccines.

The damaging data for suppression of Hib responses come from vaccines, which are not like the one under consideration today. That is a big job to extrapolate that we should have a problem because others have it. Their pertussis components are manufactured

differently. They are inactivated differently. They are formulated differently. They have different Ts. They have different Ds. They have different alum. They have different preservatives.

All of those are factors and to make the extrapolation because someone else saw 90 percent suppression, that we might also, is a very big jump and I think not scientifically founded.

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: I guess in the real world right now the kids are getting these vaccines delivered in two shots, which at least from the pediatricians I know is creating some problems and probably leading to fewer children getting all the vaccines.

In the real world, some of these kids are getting different companies' vaccines as the two components. So that we may be actually in the real world comparing a vaccine that does induce about 55 percent of the kids to develop an antibody of greater than 1, plus a very effective, as they all are, seem to be, acellular combined vaccines.

I guess I would like to keep a public health perspective on this. If we could make the leap to combined

vaccines and achieve a higher immunization rate, in the long run, that may have a better effect in terms of herd immunity and eliminating some of these pathogens.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: Can I ask a question about Slide 26? Is Slide 26, the products in this in the separate component are all the Connaught products and the only difference between the vaccine that was given in the separate and the combined is that the separate was liquid; whereas, the combined was a reconstituted vaccine?

DR. VIDOR: In the separate groups, infants received Tripedia in one arm and ActHIB at the other arm.

DR. APICELLA: Right.

DR. VIDOR: In the combined group, they received the same lots of Tripedia used to reconstitute the same lot of ActHIB.

DR. SICS: [Comment off microphone.]

DR. FERRIERI: Dr. Karzon, you had your hand up a little bit ago, a moment ago. Do you wish to say anything more? I don't want anyone to feel suppressed here at the table. We will do this as thoroughly as we can, whether or not you get lunch or not.

DR. KARZON: I think it is very possible that ten

years from now this group or its successors to us will be wondering about sporadic outbreaks of this disease. By then, perhaps, the laboratory people and the people who understand adjuvant responses and immune responses will have some more answers for us, so we can make a better vaccine.

But right now, it is one of the best vaccines that we have.

DR. FERRIERI: Dr. Apicella and then Dr. Glode.

DR. APICELLA: I am a little confused by the discussion because there were actually two questions that people are responding to. One is whether or not there is a clinical -- going to be a clinical significance if this vaccine were used and clearly the data suggest that that wouldn't occur.

The question as it is written, though, is it sufficient to conclude that the immune response to PRP is not compromised by the combination, the immune response?

DR. FERRIERI: How do you feel about this precise question?

DR. APICELLA: I do not believe that we can answer that question, given the data we have. It is right now conflicted. I would agree with the other conversation

that probably this vaccine would provide the biologic response we want to have for protection, but it doesn't answer this question.

DR. FERRIERI: Thank you, Mike. That is exactly what we are grappling with. I don't know if Dr. Frasch would agree with us or not, but we have a dichotomy going on here in terms of the responses from many members of the table.

Dr. Glode, did you want to amplify that?

DR. GLODE: I just wondered if there was even anyone here perhaps from CDC that could come in on the issue that Dr. Edwards brought up and that is of the cases that are now reported, 500 or something, that are occurring -- I just wondered, the intensity of the efforts to determine the vaccine status of each of those cases, so that if there were 50 vaccine failures this year and 150 vaccine failures next year in the 500 cases and that was due to interference, let's say, with licensure of a combined vaccine, do we have the ability to know that?

I just didn't know if those 500 cases are tracked with regard to vaccine that were administered and all that and it is possible to keep track of that.

DR. FERRIERI: Dr. Breiman, would you like to

tackle that?

DR. BREIMAN: Well, I don't know if I know the entire answer to the question. Claire, who has just come in, may have the answer or have a different perspective on the answer, but I know that within the ten population-based surveillance sites in the United States, which are quite large, there is an active attempt to determine vaccination status, but I don't actually -- I personally don't know the information about other cases from other locations.

DR. FERRIERI: Dr. Broome, do you wish to comment on that? Come up here to the table, Claire, and you can use the microphone next to Nancy.

DR. BROOME: Rob is correct that the active surveillance has the best information about both -- not only the vaccine status, but insuring that these are serotype B isolates. One of the problems with the sort of generic reports of Haemophilus influenzae is that we only get serotype information on, you know, around a half. So, it is not -- those reports are not a good way of monitoring what is going on. However, this is a priority disease for the immunization program and we are intensifying follow-up on cases of Haemophilus disease, trying to obtain information about vaccination status.

I wish I could be definitive. We looked very hard to see whether we could find any evidence of increased disease when there were concerns about immunogenicity of another manufacturer's product several years ago, as you remember. And we could not document any increased disease due to a clear decrease in immunogenicity with certain lots.

But, you know, was that negative study definitive? I think it illustrates the difficulties of being sure how easily or rapidly you could pick up a problem.

DR. EDWARDS: I think from just having a case, as well, that I know was a b, I wasn't even quite -- I know that we are one of the ten states that were reported to you and I know that that will be done, but I wasn't even quite certain. I certainly checked the vaccine records, but I wasn't sure who to call and, you know, did I call VEIRS(?), did I call CDC, did -- you know, I felt like I needed to do something but I didn't know what I needed to do. I thought maybe I needed to look at the serology in the lab, you know, and assess immune response and I think that kind of guidance for people in the trenches that is very clearly outlined is really needed.

DR. BROOME: Well, active surveillance, the name -- the whole meaning of the name is that we actually get in touch with the clinical labs and then there are folks on salary in each of those sites, who do necessary follow-up studies. So, not all of that may necessarily be visible to a clinician, but it happens.

In general, the immunization -- we will definitely be looking at whether we can do this better, but--

DR. EDWARDS: But if you want blood, I am going to have to get it, you know, in terms of the patients that are breakthroughs and that sort of thing. So, if there are issues, you know, that need to be looked at, other than the isolates,I think we need to, obviously, know that.

DR. FRASCH: From the standpoint of VIERS, failure to achieve the desired effect is a VIERS reportable event.

DR. FERRIERI: I think we need to get back on track here. We have teased this apart about as much as we can go. Is there anything else that anyone would like to say before we go around and take a vote?

Dr. Greenberg.

DR. GREENBERG: Yes. The point of immune

response. Immune response is now being defined very precisely as either GMT or percentage of people with -- or are you defining that as protective immune response? I mean, that is a definition of immune response and is a more nebulous, but maybe a helpful one for some of us who are having trouble here.

DR. FERRIERI: Dr. Frasch.

DR. FRASCH: Obviously, all we have in front of us is the geometric mean levels and the percent seroconversion to two different levels. I think what we need -- I think we need to ask this question in relation to what Dr. Fleming said, is that is -- if there is a difference, is there a clinically relevant difference?

DR. FERRIERI: Okay. We have already heard from Dr. Karzon. We will start again at the end with Dr. Eickhoff.

DR. EICKHOFF: Well, I am going to be as conflicted, as I am sure everyone else around the table is. You know, if the question were is this vaccine effective in the usual context of discussions of efficacy that we have had in this committee, I think I would probably -- I would certainly more likely than not by that 51 percent definition say "yes." And it may even be 75 or 80 percent

definition, yes. That is not the question we are being asked, however, and Dr. Frasch has chosen to draw this question much more narrowly and in a much more focused way.

I am grateful to Dr. Daum for his comments way back at the outset of this discussion, reminding us that we are not dealing here with PRP polysaccharide vaccine, but rather with a conjugate vaccine and the depth and breadth of immune responses caused by that product may be beyond our imagination, at least at this point in time. And we are looking at only one basically, one of these responses; namely, the PRP antibody response.

There may be others as well and if we accept the fact that there seems to be interference, perhaps that interference extends beyond interference simply with the PRP antibody response.

So, my answer to Question No. 4 is regrettably "no." I am not convinced that the evidence is sufficient to conclude that the immune response to PRP is not compromised.

DR. FERRIERI: Thank you, Ted.

Dr. Hewlett.

DR. HEWLETT: I feel like I am in the same position. The answer specifically to this question, I

think, given the data that we are looking at and that there are multiple unknowns here, each of which has a variability about it, which compound each other is "no." I agree with Mary Lou, however, that if we look at this as a more general question and make some assumptions about the likelihood of protective efficacy and the utility of this to the population in terms of greater level of immunization by virtue of fewer doses of vaccine, then my answer would be "yes." I think this is appropriate to use.

DR. FERRIERI: Thank you.

Dr. Glode.

DR. GLODE: My analysis would say that there were, with regard to the relevant question, two studies, a total of a 123 children, if I added right, that were given the separate vaccines and 239 given combined. The first study, I believe, does show evidence of interference. That is independent of the clinical significance of it, but scientifically, I think, it shows evidence of interference and the second did not.

So, I feel that I don't have enough numbers of children and lots of vaccine studied to understand the magnitude of the difference that may be demonstrated. So, I feel that the data are insufficient.

DR. FERRIERI: Dr. Fleming.

DR. FLEMING: Dr. David Karzon indicated, if I am interpreting correctly, that in his view the ActHIB is a very good regimen, a very effective vaccine. Mary Lou Clements pointed out that -- and I agree with her as well-- that it is critical to keep a public health focus here, to look at what is the public health impact of what a decision such as this could mean, i.e., any change that we make from what Dr. Karzon refers to as a very effective vaccine, we need to be reasonably confident will still maintain much of that benefit that we are already achieving.

If we were to use what has been put forward as a key surrogate in this setting, which is achieving a level of 1, the data are suggesting that as the historical data showed that with the separate administration, you get about 90 percent. With the combined, there is a reduction estimated to be on the order of 10 percent, from 90 to 80, where confidence intervals don't allow us to rule out that there could be as much as a 15 to 20 percent reduction. However, this endpoint, as we have heard, this surrogate may not, in fact, probably likely is not a fully adequate surrogate to really capture the essence of what level of protection we are achieving.

But then if we step back from this, the question is then what is the scientific basis upon which we are going to draw our conclusions. There certainly is evidence of some interference. What I am still very unclear about is what level of interference would we have -- would we have had to have seen in order to say that is not acceptable.

And it seems to me in conclusion then, just to go back to Mary Lou Clements' earlier comment, the issue of likely increase and use of a vaccine is important but it is still somewhat speculative as to what that would be. And, again, I am left with very relevant considerations being put on the table, but in the absence of clear information upon which to make a reasoned decision or reasoned judgment -- so, it is on the basis of that lack of clear information that I have no alternative but to not be able to say that the data are sufficient to conclude that the immune response is not compromised.

I don't have the scientific basis upon which to draw that conclusion.

DR. FERRIERI: Thank you, Tom. I think that you can gather from everyone else's remarks that we are also in a muddy situation.

Dr. Villalta.

DR. VILLALTA: I agree with Dr. Fleming really but, nonetheless, I also balanced both points. We have a variation here from 70 to 90 percent response to this polysaccharide and another variation from 60 to 90 percent. We don't know the mechanisms that caused this particular variation. We don't know if this a different response of infants or whether or not it is in the parallel of the vaccine.

I was worried if really there is a suppression. If the response to this Haemophilus b polysaccharides is opposed, but I really don't have any certainty to say whether or not the variation is going to affect the efficacy of this particular vaccine, but on the other hand, I am consistent with what was mentioned really that this is up to a new technology, up to the new strategies, to always recommend that these vaccines might serve the mission of the public for this time.

DR. FERRIERI: Thank you.

Mrs. Cole.

MS. COLE: This is really hard for me. I want to see a real good, good combination vaccine out there because there would be a greater number of immunizations, but at

the same time, we don't know what a compromise could be acceptable, you know, what amount, how far can it go. So, I am going to have to say "no" as far as the question goes as written.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: It has all been said. I am not going to repeat it. I would say "no."

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: I am going to say "no," but I think I am saying "no" to a clinically insignificant problem as it is posed. So, I personally, based on the historical record -- now, this is not my field, but looking at the historical record, I would say that the clinical significance of my saying "no" is minimal. I think this vaccine is perfectly acceptable clinically. So, I don't know how staff uses this decision. The way it is formulated, the answer is "no," but I really think -- the other part of your question, what is clinically relevant, is really what we are all about here, not some fine point of statistics.

I haven't heard all the data, but from what has been presented, this vaccine, the reconstituted vaccine, looks like it will be clinically useful.

DR. FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes. I would like to give my response in light of what I thought I interpreted Carl saying and that is is there data for the immune response to Haemophilus influenzae sufficient to conclude that a clinically significant immune response to PRP is not compromised and I think, you know, that there is comparability in terms of the percentage of children who achieved seroconversion, that there is some difference, albeit, I think, insignificantly clinical difference in terms of their achieving the level of 1 microgram per mL. The GMTs achieved are less but they are within the range of what has been found to be acceptable for licensure of the separate products.

So, I would like to vote that they are "yes" to conclude that the immune responses are of no -- they are different but not of clinically significant difference.

DR. FERRIERI: Thank you.

Dr. Poland.

DR. POLAND: The question is a narrow and focused one, but the data is not. I guess I feel that there is evidence to suggest that the immune response is compromised. The question is is that clinically relevant?

That is a testable hypothesis, albeit, maybe not in the United States, but it is possible. We have also heard a lot about variability in response. I am also confident that that variability can be quantitated and we can determine whether that variability is significantly greater in a combined versus separate administration schedule.

So, taking the narrow question then, I vote "no."

DR. FERRIERI: I vote "no" also but I would like to summarize how I perceive the committee's responses, Dr. Frasch. There is a level of discomfort about interpreting the differences seen. There are concerns about the inadequacy of numbers in the trials that led to the data that we saw. We see a mixture of lots making it difficult for us to truly interpret the scientific data.

On the other hand, there is great concern in trying to reconcile these problems and to respond to the public health need for combined vaccinations. So, I will take the prerogative of directing you and the Agency to reexamine all of this with the sponsor to see whether or not you can respond to all of the concerns that have been articulated over the past hour and a half or more on the vaccine.

If you have any further comment, fine. But I

think that the transcript of our deliberations when read will give you the direction that you need.

DR. BREIMAN: If I could just say that I think that to some degree what the committee has been considering today, the data that were presented were really not what ultimately the committee needed to consider the real issue, which is what is clinically relevant. And it might be helpful to summarize also what the questions are that need to be answered in order to best assess that. I think people have highlighted a number of things, including, you know, what level of variability there is in the assays, but also I think probably more importantly I think we need to have more of a sense of how antibody levels correlate with carriage, with disease.

You know, as been said, I mean, having additional data on failures, you know, vaccine failures would be useful and we actually didn't hear anything at all about duration of antibodies. You know, I think that that also would be important in having some way to look at how -- whether or not there is a difference in the primability, if you will, of the cells. Are they more or less likely to respond appropriately, given, you know, a challenge.

You know, to some degree, a lot of those data may

already be there. I mean, Dr. Sics presented, I think, some interesting data just off the cuff about the company's own product in Germany and how levels of antibody correlated with reduction of disease and those levels of antibody were markedly less than what we usually consider.

So, I think it -- in a way the question is different than what we initially examined and it might be useful to, you know, have a good sense of what kind of data you now need in order to best assess these questions.

DR. FERRIERI: Thank you, Dr. Breiman.

DR. FRASCH: If I could sort of -- what I understand you have said is that you have not been able to say that there was not an interference, but that the data that you have actually seen, the differences were probably not clinically relevant or important.

DR. FERRIERI: Well, some members of the committee said that, Carl, but not everyone. So, I wouldn't take that away as the strongest message. We don't know whether the differences would be relevant. There are guesses by some members of the committee that they may not be and there is an inclination to think they probably are not. But we don't have a firm grasp of that.

This is not easy and if we seem to be non-

decisive today, I don't feel that it is because of our lack of trying. We have really tried very hard, everyone, and I think the Agency and the sponsors have done a great job in trying to open up the issues for us. I think that maybe six months from now and a year from now, we won't have more to guide us, Dr. Breiman, and some of the issues you have brought up have been tackled here over the past several years without having an answer. So, we have gone around and around on what is a protective level and so on and so forth.

Carl, I think time must be considered here. We are convening again this afternoon at 1:30 sharp. We will be starting half an hour late, so people can get refreshed and have a bite to eat for the next session.

Thank you all very much.

[Whereupon, at 12:50 p.m., the meeting was recessed, to reconvene at 1:30 p.m, the same afternoon, Thursday, June 5, 1997.]

A F T E R N O O N S E S S I O N [1:30 p.m.]

DR. FERRIERI: Good afternoon, everyone. If you could please have a seat so that we can start the second session. This is an open session on adult pertussis. It is sort of an ongoing theme of the day, as you well know.

I think we are all energized by our break so that we can put our very best talents to this subject and do justice to the sponsor, as well as to CBER.

We will start with Dr. Burns, Dr. Drusilla Burns from the FDA CBER, who will introduce the subject and then move the program along.

Agenda Item: Introduction

DR. BURNS: This afternoon we are going to consider what kind of data we need to support the efficacy of adult pertussis vaccines. For many years now, pertussis vaccines have only been given to children up to seven years of age. The reason for this is probably several fold. First of all, the disease in adults, until recently, was thought to be a rare occurrence and when it did occur, the disease was thought to be relatively benign.

Also, until recently, the only vaccine that we had to give was the whole cell vaccine, which was associated with some local and systemic reactions. And,

therefore, the risk of pertussis vaccinations in adults was thought to outweigh any benefit that they may gain.

However, with the recent development of the safer acellular pertussis vaccines and with increasing recognition of adult pertussis, the medical community is now reconsidering the use of adult pertussis vaccines.

The discussion today will be generic. We are not going to consider a particular vaccine, but we are posing the questions concerning what kind of data we need to pertain to all applications that we might get in the future. What we thought we would do today is before we begin -- before the committee begins the discussion of the questions that I will pose after the break is to give everybody a little bit of background about pertussis in adults.

We will start with a talk by Karen Farizo, who will talk about the epidemiology of pertussis, including pertussis in adults. She will touch on the type of disease that adults get and also will touch on what little is known about transmission of pertussis from adults to very young children.

Then I will review the data on the efficacy of acellular pertussis vaccines in infants, in case any of you

have missed the last eight meetings that we have had, and after that, Wendy Keitel will show some data that she -- some immunogenicity data, where she examined acellular pertussis vaccines in adults.

We will then have the break and then several manufacturers have requested to speak, to show some data that they have that pertains to this subject.

Finally, then, we will get into the questions.

So, we will start with Karen Farizo, who is from the FDA.

DR. FERRIERI: An interruption for an urgent announcement Mrs. Cherry will make.

MS. CHERRY: Is there a Dr. Marcel Solard(?)? I have a message for you.

PARTICIPANT: He just went back to the office.

MS. CHERRY: Okay. Thank you.

Agenda Item: Epidemiology of Pertussis in Adults

DR. FARIZO: As you have heard from Drusilla, the purpose of my presentation is to review what is currently known about the public health burden due to pertussis in adolescents and adults in the United States.

I will begin with a review of recent trends in the National Surveillance Data and then I will present some

of the major findings of relevant epidemiological and serological studies of pertussis, discuss the spectrum of disease due to pertussis in adolescents and adults and the role of adolescents and adults in the transmission of pertussis to infants.

Because of time constraints, I will only be able to highlight the major points and common themes in the literature, using data from published representative studies.

In the pre-vaccine era, pertussis was the major cause of morbidity in the United States. Then following the introduction and widespread use of whole cell pertussis vaccines in the mid to late 1940s, the incidence of pertussis declined dramatically, initiating a trend that continued for nearly 30 years.

Although the annual incidence of pertussis had been reduced by 99 percent by 1970, rates began to stabilize over the next decade. During the 1980s, as best shown in the insert, the annual number of reported pertussis cases began to increase, a trend, which has continued thus far in the 1990s.

Now, although the recent peaks are consistent with the previously observed three to four periodicity in

pertussis incidents, it is clear that the number of reported cases has steadily increased. This increase likely reflects to some extent increased recognition and awareness of pertussis and increased diagnostic efforts.

However, the general consensus among public health officials has been at least some of this apparent trend likely represents a true increase in disease.

Now, in evaluating this increase, it is useful to examine age-specific incidence data, which are shown on this slide for the years 1980 through 1996. And it becomes apparent that the increase in incidence of reported pertussis has been most pronounced in adolescents and adults, as shown by the blue line, the pink and the white line at the bottom, compared to the relatively flatter curves at the top of the graph for infants and young children.

Now, underreporting in general is a well-recognized limitation of the National Surveillance Data and reported cases disproportionately consist of clinically obvious classic and severe cases, which tend to occur more frequently in infants and unvaccinated young children. Thus, the completeness of reporting is thought to be lowest among adolescents and adults.

Nevertheless, it is well-recognized that the risk for significant pertussis illness remains highest among infants, as reflected in these data. On average, infants have accounted for approximately 40 percent of all reported cases in the past several years in the U.S. And of infants with reported pertussis, approximately 80 percent were younger than six months of age. Thus, many infants with pertussis are too young to have been fully protected with three doses of pertussis vaccine and to prevent disease in these infants, additional strategies, such as booster vaccination of adolescents and adults, as well as earlier vaccination of infants, have been proposed.

Nevertheless, in recent years, nearly half of infants and preschool-aged children, who were old enough to have received three doses of pertussis vaccine, were under-vaccinated. Thus, timely vaccination of infants and children remains an important focus of primary prevention efforts.

Now, returning to pertussis in older age groups, in addition to the National Surveillance Data, there are several other lines of evidence, which indicate that the burden of pertussis in adolescents and adults may be considerably greater than previously appreciated. Over the

years, pertussis rarely has been documented in the U.S. as a cause of large outbreaks of cough illness among adolescents or adults.

In the 1980s and 1990s, there have been reports of outbreaks of pertussis in which a large proportion of cases were in previously vaccinated adolescents, who also had relatively high attack rates. One of these was a community outbreak in three counties in Wisconsin in 1985, in which approximately one-third of 161 culture positive cases were in adolescents, who had the second highest attack rate after infants.

Other pertussis outbreaks have occurred in school settings, including a small outbreak in classroom in Missouri in 1991 and several school outbreaks in Massachusetts, where surveillance efforts have included increased investigation of outbreaks of cough illnesses in schools.

One of these involved 218 students in a middle school and a high school and in that outbreak most of the cases were diagnosed only on clinical grounds without laboratory confirmation. Thus, the contributing role for other respiratory agents could not be excluded. However, this investigation suggested that pertussis may cause large

outbreaks among adolescents.

Now, because of the problems with the conventional methods for diagnosing pertussis, namely, the low sensitivity of culture and the variable sensitivity and specificity for direct fluorescent antibody staining or DFA staining of nasopharyngeal secretions, there has been much interest in the use of serological diagnosis of pertussis to better estimate the burden of disease in adolescents and adults.

In several of the slides to follow, I will be presenting data from studies in which serologic methods for detecting Bordetella pertussis infections were used. And I won't have time to present the methods for each study in great detail and certainly an evaluation of the serological assays used in these studies is beyond the scope of this presentation. However, in reviewing these data it is important to keep in mind that the accurate serodiagnosis of pertussis in adolescents and adults is complex in that assays, methods and definitions have varied among studies.

While there is general agreement that demonstration of a significant change in antibody level to pertussis toxin is a reliable means of diagnosing pertussis, further evaluation of the specificity of some of

the other assays for other antibodies and of the use of single serum specimens is needed.

So, with that in mind, we will turn to some of the data.

The Massachusetts Department of Public Health provides a free diagnostic service for pertussis to physicians and the hospitals statewide. This service has included culture and DFA staining of nasopharyngeal secretions.

Then in 1987, the Massachusetts state laboratory initiated serologic diagnosis of pertussis, using a single serum anti-pertussis toxin IgG ELISA in persons 11 years of age and older. During the four year period, 1988 through 1991, the addition of this serologic criterion increased the incidence of reported pertussis in this age group approximately fourfold, from 3 to 12.9 per hundred thousand in adolescents and from .16 to .56 per hundred thousand in adults.

There have also been several prospective case series in the U.S. in which adults presenting to a health care facility with persistent cough were evaluated for pertussis by both bacteriologic and serologic methods. In these studies the reported prevalence of Bordetella

pertussis infection among adults with persistent cough ranged from 12 percent to 26 percent. And although paired sera were collected on some patients in three of these studies, in most instances the serologic diagnosis was made on the basis of a single serum specimen in which the antibody level to one or more specified antigens was significantly elevated above levels obtained for a control group.

Now, using the data from the study in the HMO, which was conducted in San Francisco in which single serum anti-pertussis toxin antibodies were used, the authors estimated that the annual incidence of adult pertussis in the patient population was actually several hundred fold higher than that which is reported at the local or national level.

And as some of you have heard this morning, results generally consistent with these also have been obtained from a study in an HMO in Minneapolis, where adolescents and adults with cough are being evaluated. Taken together, these studies not only demonstrated the low sensitivity of culture for the diagnosis of pertussis in this age group, but also suggested that pertussis may be a more common cause of persisting cough among adults than

previously appreciated.

So, what are the clinical characteristics of pertussis in adolescents and adults? As expected, cough is the most common symptom. The illness is generally prolonged, often lasting more than three weeks. More than two-thirds of adolescents and adults with pertussis have reported that the cough was paroxysmal or spasmodic in nature. However, there are no clinical features which reliably distinguish pertussis from other cough illness in adolescents and adults.

The reported frequencies of some of the classic signs and symptoms of pertussis, as well as of the severity of the disease in adolescents and adults, has varied somewhat across studies. It seems that overall severe disease does not seem to be the typical presentation.

Serious complications and hospitalizations have been reported but occur relatively infrequently and deaths due to pertussis in adolescents and adults are rare.

Serological studies in healthy individuals also suggest that sub-clinical Bordetella pertussis infections may be relatively frequent in adolescents and adults. And in two recent longitudinal studies, one in adolescents and one in young adult health care workers without known

exposure to pertussis, consecutive serum samples were tested for pertussis antibodies and depending on which antibodies were considered and depending on the definition of "seroconversion," the predicted annual incidence of Bordetella pertussis infections among the adolescents ranged from 1 to 8 percent and the average annual rate among the adult health care workers ranged from 8 to 33 percent.

There also have been pertussis seroprevalence studies in health persons and in one study of persons ages 1 to 65 years, two peaks in pertussis toxin in FHA antibody levels were observed; one in children ages four to six years, concurrent with the administration of booster doses of pertussis vaccine, and a higher peak in adolescents, suggesting that pertussis infection may be relatively frequent in this age group.

In the second study, U.S. university students and German military recruits had similar levels of IgA antibody to four pertussis antigens. Now, since IgA antibody results mainly from infection and not from immunization, these results suggested that pertussis infections may be common in young adults in the United States, given the much higher incidence of clinical disease in Germany, where

routine vaccination has only recently been recommended.

Finally, in a study of young adults employed in an emergency room, most had pertussis toxin and FHA antibody levels that were substantially lower than levels commonly seen in children or adults following immunization. And although there is no diagnostic cutoff value for PT or FHA antibodies that can be used to determine pertussis immunity, these results suggested a high level of susceptibility among these health care workers, who may be at risk for coming into contact with pertussis and transmitting it to susceptible patients.

So, these recent epidemiological and serological studies taken together with the National Surveillance Data have heightened concerns about increasing susceptibility to pertussis among older age groups due to waning immunity. In examining the Surveillance Data, it seems that most persons who were born after 1950 in the United States, and particularly those born after 1970, which would include young adults and adolescents, were likely to have acquired immunity to pertussis from vaccination, with natural infection playing a less prominent role.

Fewer exposures to pertussis, which may have resulted in natural boosts in immunity, combined with

gradually waning vaccine immunity, may have led to an increased pool of adolescents and adults, who are susceptible to pertussis.

Now, the interest in booster doses of acellular pertussis vaccines for adolescents and adults is driven in large part by concerns that this age group may be an important reservoir of infection for infants and available information on patterns of transmission of pertussis obtained from household studies of pertussis are presented in the next couple of slides.

Perhaps the most frequently cited study on the transmission of pertussis from adults to infants was a retrospective review of pertussis cases confirmed by culture or DFA that occurred in Dallas during a 12 year period in the sixties and seventies. In that study of infants for whom source of infection was documented, 15 or 54 percent acquired infection from an adult.

In that same column, in two household transmission studies, one conducted during the outbreak in Wisconsin in 1985 and one conducted in Finland, transmission of pertussis from adolescents or adults to infants was documented but the number of infants reported on in these studies was small.

There also have been several reports of a substantial proportion of primary cases of pertussis in households occurring in adults or adolescents. In addition to these household studies, there have also been a handful of reports of neonatal pertussis in which an ill mother was the likely source.

Also, in the 1970s, there were a few reports of small outbreaks of pertussis in health care settings with nosocomial transmission from adults to infants documented. While there may be others, I am unaware of more recent published reports of nosocomial transmission to infants.

In a case control conducted during the pertussis outbreak in Chicago in 1993, young maternal age and a history of cough in the mother were risk factors for pertussis in young infants. In a recent household study in Germany, spread of pertussis was just as likely in households with an adult primary case as in those households with a child primary case.

Finally, in a study in Los Angeles, most index cases or the first recognized cases in households were in infants or young children. However, further investigation indicated that only about a fourth of primary cases who were responsible for introduction of pertussis into the

household were in infants and young children. And approximately half were in adolescents or adults.

So, in summary, although the actual incidence of pertussis in adolescents and adults in the United States is not known, there has been an apparent increase in pertussis in these age groups in recent years. The increase is possibly due, in part, to decreased natural immunity and waning vaccine-induced immunity.

Although reported pertussis in adolescents and adults usually is not severe, the cough illness is typically prolonged, lasting several weeks.

Finally, although available data have demonstrated a role of adolescents and adults in transmission of pertussis, the extent to which such transmission contributes to the overall burden of pertussis in infants is not known.

DR. FERRIERI: Are there any questions for Dr. Farizo?

Dr. Apicella.

DR. APICELLA: Has anyone looked at this question using something like PCR to identify presence of the bacteria in respiratory secretions?

DR. FARIZO: In fact, at least some of the

studies in which both bacteriologic and serologic methods were used, PCR was also used in some of the patients. Just as with serologic diagnosis of pertussis, adding PCR does seem to add to the number of cases over that which is confirmed by culture alone. But I don't think we have any more conclusive data about the incidents of pertussis by adding PCR to the diagnostic efforts.

DR. FERRIERI: Yes, Dr. Greenberg.

DR. GREENBERG: How sure are we that the serologic diagnosis is accurate? That is, that people have tried to culture and there is always a sero response that there aren't other antigens in the environment that could lead to immune responses that would be read out as pertussis-type responses.

DR. FARIZO: As I mentioned, the serologic diagnosis of pertussis is quite complex and relatively new and certainly I think there is general agreement that demonstrating a significant rise in antibodies to pertussis toxin is a reliable method for diagnosing pertussis. However, in many of these studies, it is not possible to get acute and convalescent sera. So, people have also looked at the usefulness of single serum specimens and much of the data on serology that I have presented, the increase

in the number of cases or the -- a lot of the patients who were classified as having serologic evidence for infection, those diagnoses were made on the basis of a single serum specimen.

In all of these studies, there has been a control group. So, there is a lot of questions about how much higher than the control group is really reliable. So, the specificity of using single serum specimens in general, I guess, is somewhat open to question.

There are also some concerns regarding specificity to antigens -- antibodies to antigens other than pertussis toxin and cross reactivity to other organisms. Certainly, other species of Bordetella, besides Bordetella pertussis, produce FHA-like molecules and there may be some cross reactivity with peri-pertussis antigens and antibodies to FHA. There has also been a report of monoclonal antibodies to FHA immunoreactive with high molecular weight outer membrane proteins of non-typable H-flu.

DR. FERRIERI: Any other points? Otherwise we will move on -- Dr. Fleming, again.

DR. FLEMING: The contrast between the serological data and the epidemiological and National

Surveillance Data is quite striking, where you had begun with the National Surveillance Data showing rates in adolescents and adults of 1 down to .3 cases per hundred thousand per year and then we evolved through your discussion to the point near the end where the serological data was reflecting subclinical levels detectable in up to 10 percent, which is 10,000 fold greater.

I guess my first question is -- that is really striking -- can you comment on that? Then, secondly, how do we proceed from here subclinical disease that would never be clinically diagnosed? If that is the vast majority here, how important is it to control that?

Now, you have mentioned one of the reasons and that is it may be transmission to infants, although it is not clear at what level of disease you would need to have to be infectious. I don't know how much we have gotten to that. So, there are really the two questions for you.

DR. FARIZO: I think in addition to what appears to be a very high incidence of subclinical infections, there were some data presented on patients who actually have cough illnesses. Then the serologic diagnosis seems to be increasing the estimated incidence about a hundred fold over than what is reported. So, there does seem to be

-- the serologic diagnosis is seeming to not only add a large pool of subclinical infections, but also some amount of true clinical disease and these patients who do have cough illnesses and have serologic evidence for infection are truly coughing for prolonged periods.

DR. FLEMING: So, does that mean, if I followed what you said, that the actual not subclinical but symptomatic disease may be on the order of a hundred times greater than the .3 to 1 per hundred thousand that the Surveillance Data would show? Is that what you were saying?

DR. FARIZO: That is what I am saying, that the available data that we have from non-population-based studies would suggest that. The only population-based data that I presented were those from the State of Massachusetts.

DR. FLEMING: So, that would be 30 to a hundred per hundred thousand or one case per 1 to 3,000 person years.

DR. FARIZO: I think that is right.

DR. FERRIERI: Dr. Broome, the last question.

DR. BROOME: I am interested in whether any of the studies give us any information about at least whether

the whole cell vaccine has much effect on the occurrence and circulation of -- if we accept a certain level of minimally symptomatic or adult disease. I guess one way to look at that would be -- you sort of did middle school and high school attack rates. What if you go down into elementary school -- you know, is there anything which lets you say that, well, it is only 10 to 15 years after your last booster that we start seeing this disease?

DR. FARIZO: I think that the available data would suggest just what you said. There doesn't seem to be an increased problem among younger children; example, five to nine years of age. And certainly in the National Surveillance Data the curve for the five to nine year olds is relatively -- I guess I am not answering your question.

DR. BROOME: Well, I guess I don't put a lot of weight on the National Surveillance Data, I am sorry to say. I am talking about systematic studies where you do periodic bleeding from --

DR. FARIZO: I think that in most of the studies that have been done, people have really focused on adolescents and adults. The one study in which serum specimens were collected on people from infancy to age 65 did not seem to suggest that there is a problem in the five

to nine year olds. The problem was first -- seemed to first surface in adolescents, but I am not sure people have looked really hard, as hard in younger children as in adolescents.

DR. FERRIERI: Thank you, Dr. Farizo.

We will move on to the summary of efficacy data in infants. Other questions can emerge later during the committee discussion period.

Agenda Item: Summary of Efficacy Data in Infants

DR. BURNS: Since the first question that we are going to ask the committee to address is whether you can use efficacy data that came from infant clinical trials to support the efficacy of adult pertussis vaccines, I thought I would I would review the information that is available on the efficacy of these vaccines in infants.

This committee has seen a lot of data over the last two years and what I thought I would do is just go over the efficacy information for the six vaccines that this committee has seen at one time or other over this two year period.

I am going to start with the least complex of the acellular pertussis vaccines and that is the one manufactured by Amvax. It is a single component vaccine

composed of inactivated pertussis toxin. Of course, in these trials the pertussis component was combined with diphtheria and tetanus toxoids.

The trial for this vaccine was in Gothamberg(?), Sweden. It was a prospective randomized double blind trial, in which the acellular vaccine was compared to a placebo control. There were about 3,400 infants in the trial and the dose regimen was three, five and twelve months of age.

The case definition that was used in this trial really describes what we consider fairly severe pertussis; at least 21 days of paroxysmal cough, plus culture serology or contact and the vaccine efficacy measured for this vaccine had a point estimate of efficacy of 71 percent and I also show the 95 percent confidence intervals.

Moving on to the two component vaccine that actually we heard a little bit about today, this morning, this vaccine is pertussis toxoid and FHA, manufactured by Connaught Laboratories, Incorporated. It goes by the name of Tripedia. This vaccine was studied in several trials and the first of these trials was in Sweden in 1986 and 1987. It was a prospective, randomized, double blind, placebo-controlled trial.

Two doses of the vaccine were given; the first dose at five to eleven months of age, followed by a second dose, eight to twelve weeks, the later. They had two definitions of disease that they used in this trial. One describes really not what you wouldn't consider very -- includes mild disease. It is positive culture with any cough. The second one is positive culture with more than 30 days of cough, so more severe disease.

Vaccine efficacy for the primary analysis was 69 percent and for secondary or the more severe type of disease was 79 percent.

We have a three component vaccine manufactured by Chiron. It is composed of pertussis toxoid, FHA and pertactin. This vaccine was studied in the Italian efficacy trial that actually this committee heard about about two years ago when the trial was first over. It was a prospective, randomized, double blind trial and included two acellular pertussis vaccines -- and I will get to the second one next -- a whole cell pertussis vaccine and a placebo.

About 15,000 infants were in this trial. The vaccine was given at two, four and six months of age. Again, they used a fairly severe definition that would

describe fairly severe pertussis, 21 days of paroxysmal cough, plus positive culture or positive serology and it had a point estimate of efficacy of 84 percent.

The second vaccine in the same trial was another three component vaccine, manufactured by SmithKline Beecham and was recently licensed in January of this year. It had a point estimate of efficacy of 84 percent also.

The Wyeth-Lederle vaccine, which is actually composed of four components, the three that I have talked about previously and Type 2 fimbriae. This vaccine was studied in a trial in Germany. There were actually two strata and the committee heard about this vaccine last October and the vaccine was licensed in December.

In the first stratum, the acellular was randomized versus the whole cell vaccine and in a second, non-randomized group were children whose parents declined to get a pertussis-containing vaccine. So, they received DT alone. There were 10,000 infants in this trial. There were four doses given, three, five and seven months of age with a booster at seventeen months. Again, the definition was fairly severe pertussis, at least 21 days of cough with paroxysm, whoops or vomiting, plus positive culture, positive serology or contact.

After three doses, the vaccine efficacy was 73 percent and after four doses it was 85 percent.

Finally, a five component vaccine that contains both Type 2 fimbriae and Type 3 fimbriae. This was in a trial conducted in Stockholm, Sweden that ended about two years ago, when the committee heard the data from this trial. In this trial there were two acellular vaccines, a whole cell vaccine and a placebo control. There were 10,000 infants who received the vaccine at two, four and six months of age.

The definition of disease was at least 21 days of paroxysmal cough, plus positive culture, positive serology or contact and the vaccine efficacy was 85 percent.

So, in summary, we have seen a lot of acellular pertussis vaccines and all of them had a significant efficacy in the infant population.

As Karen Farizo just told you, pertussis in adults often presents as not as severe a disease as is observed in infants. So, the question comes up do acellular pertussis vaccines protect against less severe disease as well as more severe disease. We can get some information concerning this question from the efficacy trials that I just described.

For instance, in the Italian trial, in addition to the primary case definition, they looked at secondary definitions, which included any cough greater than seven days for laboratory confirmed disease. In that case, both of the three component vaccines that were in that trial still had significant efficacy against pertussis; 71 percent was the point estimate for both vaccines.

In the Swedish trial, which had the Connaught Labs limited five component vaccine, this vaccine had an estimated efficacy of 78 percent against laboratory confirmed pertussis with at least one day of cough.

I want to remind everybody -- I mean, the trials were, I would say, quite successful in many ways, but one disappointment of these trials was for the fact that there was no serological correlate of protection emerging from any of these vaccine trials.

There now is interest in adult vaccines and clinical trials have begun. You will hear about some of these today, including safety and immunogenicity studies, pertussis vaccines in adults. And in addition, there is an efficacy trial that is planned and it is about ready to start.

This trial is sponsored by NIAID and I wanted to

go over some of the goals of this trial. Of course, it will evaluate the protective efficacy of a single acellular pertussis vaccine, given as a single dose in individuals who are 15 to 65 years of age. Because of the age of these individuals, they will have either never been vaccinated as children or will have received a whole cell pertussis vaccine.

Now, I bring this point up for a reason because I think we have a moving target here of what type of individual we are going to try and protect in the future. In 1991, the first acellular vaccine was licensed as the fourth and fifth dose. So, that cohort of kids will come into adolescence probably in just a few years.

After that comes another cohort of kids that will have received acellular vaccines for all five doses.

The second and third goal of the NIAID trial, I think, are very important and, I think, I have heard David Klein, who is here today to answer any questions you might have about this trial, are very important goals of this trial. They are to characterize the spectrum of illnesses caused by b pertussis in adults and adolescents and to determine the incidence of b pertussis infections in adolescents and adults.

Finally, of course, they will get safety and immunogenicity information from the vaccine.

DR. FLEMING: Excuse me. Will you be commenting a bit more on the design of this trial? What we will learn about efficacy?

DR. BURNS: Barbara Howell from SmithKline Beecham will go over the design of the trial in the manufacturers' presentations. And David Klein is here to answer specific questions that you might have.

I want to be careful and not -- I know it is important that everybody understands about that trial, but I don't want to dwell on that trial because I think we have a very generic question to ask and that is what kind of efficacy data do you need, not anything specific. We don't want to dwell on the NIAID trial per se. But Barbara Howell will go over the design.

So, what will the NIAID study not answer because it is not designed to answer these questions. First, it will not answer what the duration of protection is and, secondly, it will not tells us about transmission of the disease from adults to children.

So, that is the end of my presentation. If anybody has any quick questions that I could clarify?

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: You passed over the safety data in children pretty quickly on those studies, but as I remember there was some data that suggested that the more doses the child received, the more side effects they had.

DR. BURNS: That is true.

DR. APICELLA: And there was a question about five doses and what you could expect.

How does this figure into the fact that you are going to get a cohort of children in eight years who are going to have had acellular vaccine and then you are going to vaccinate them again as adolescents?

DR. BURNS: Wendy Keitel might be able to answer this question specifically. I mean, she has done a study in adults, but, of course, those adults received the whole cell vaccine. So, we don't have any information on kids that got five doses of acellular and then as an adolescent, got a booster dose. But I think that manufacturers have taken this problem into consideration.

Obviously, it is a problem with, and it has always been a problem the diphtheria component of the TD vaccine. And for that very reason because of reactions with repeated doses of diphtheria toxoid, they lowered the

dose of diphtheria in the TD vaccine. And I think that is what several manufacturers are considering.

We may not have the full pediatric dose in the adult vaccines, but I think that is going to be something that we need to address on a case-by-case basis, depending on which vaccine that we are talking about. I don't know if we can really quite generalize to all vaccines yet.

DR. FERRIERI: Dr. Daum.

DR. DAUM: Drusilla, I got a little confused about your conclusion about the business of mild disease. I thought you showed when you were going through the trials a slide of the Connaught two component vaccine, where they had two estimates of efficacy, one with a cough of more than 30 days and one with any cough, implying that more severe disease had a higher efficacy estimate in that trial.

Then I thought you showed some other data subsequently, which suggested there wasn't a difference between mild disease and more severe disease.

DR. BURNS: There still was a difference if you look at the exact numbers. In the Italian trial for the very severe disease as point estimate of efficacy for both vaccines was 84 percent and it went down to 71 percent when

you include the milder disease. So, there is still a difference.

DR. FERRIERI: Dr. Snider -- I am sorry. I interrupted you.

DR. DAUM: Just one quick follow-up.

I was really involved with the original sort of -- the first Swedish trial way back in the mid-1980s and there the efficacy estimate for culture proven pertussis varied pretty impressively with the degree of clinical involvement that went with that positive culture and cough. And I came away, I guess, believing that the acellular vaccines, like probably the whole cell vaccines before them, did protect against more severe clinical disease better than more mild disease.

I wonder if you would comment on that.

DR. BURNS: Well, that is actually the numbers I showed. If you have laboratory confirmed pertussis for a cough of 30 days, it was 79 percent and the cough -- any cough was 69 percent. So, it did go down.

DR. SNIDER: Dr. Burns, I wonder if you could remind us of the duration of follow-up in these various studies? What happened to efficacy over time? Also, whether any of the study populations are still under

observation or the possibility that they could be looked at again?

DR. BURNS: We may -- to a certain extent, the answer to that question is vaccine specific. In the Italian trial, they have followed up for a fair amount of time and depending -- both vaccines actually still have over -- I think it is 18 months or two years follow-up after the end of the trial. There is still significant efficacy.

In one vaccine -- I don't know, maybe the people from SKB or Chiron would want to talk about their vaccine specifically?

DR. EIDEN: I am Joe Eiden representing Chiron vaccines.

In the Italian efficacy trial follow-up is ongoing but through at least three years of age, efficacy is sustained for both of the acellular pertussis vaccines. For the Chiron vaccine it is at 89 percent through three years of age. That is with no additional pertussis vaccine doses being given in the second or third year of life. That is based upon the three dose series at two, four and six months of age. In that study, they are still continuing to follow efficacy through additional years.

DR. FERRIERI: Those were comments of Dr. Joseph Eiden for the transcriber.

Dr. Jo White.

DR. WHITE: Jo White, Amvax.

It was just published from the Yotaborg(?) study for up to three years of follow-up after three, five and twelve months and the vaccine efficacy was 77 percent. So, it did not decrease over time, at least that time period.

DR. FERRIERI: Any comments before Dr. Keitel's presentation?

[There was no response.]

I think we must move on then.

Dr. Wendy Keitel from Baylor will present on the immunogenicity of acellular pertussis in adults.

Agenda Item: Immunogenicity of Acellular Pertussis in Adults

DR. KEITEL: While most cases of severe and fatal disease caused by Bordetella pertussis occur in infants and young children, the occurrence of infection and disease in adults is increasingly recognized, in recent years the incidence of reported pertussis in adolescents and adults has been rising.

Outbreak investigations and family transmission

studies confirm higher infection rates in adults and adults often are responsible for transmission of infection to infants in these settings.

Several prospective studies have indicated that Bordetella pertussis is responsible for about a quarter of prolonged cough illnesses in adults, based on serologic response to the organism. Waning immunity after immunization in childhood appears to contribute to the occurrence of pertussis in adults.

These data suggest a potential need for booster immunization of adults after childhood to control pertussis in adults and children more effectively.

No current recommendations exist for routine use of pertussis vaccines in adults. In some studies, immunization of adults with whole cell pertussis vaccines has been associated with moderate to severe local reactogenicity and unacceptably high rate of fever and occasional generalized skin rashes.

In contrast, numerous studies have demonstrated safety and immunogenicity of acellular vaccines in adults. However, most studies in adults have been designed with the needs for primary immunization of infants in mind.

The purpose of our study was to compare several

acellular pertussis vaccines with the needs for booster immunization of adults as the primary focus. In view of the consideration that affective reimmunization of primed adults likely will require lower doses of antigen, limited dose response evaluations were conducted.

Healthy 18 to 45 year old adults were invited to participate in a multicenter, double blind, placebo-controlled clinical trial. Only persons with no history of pertussis or immunization against pertussis within the past ten years were eligible for participation.

Five acellular vaccines were studied, placebo with saline with thimerosal.

The composition of the highest dose of each vaccine studied are shown in this slide. The diverse methods of inactivation of the PT have been described previously and just for review here, the Amvax vaccine was -- the PT was inactivated with hydrogen peroxide, in Massachusetts, with tetranitromethane(?), the Biocine with genetic and a small amount of formaldehyde, SKB with glutaraldehyde and formalin and Connaught with glutaraldehyde.

Note that vaccines containing two, three or four plus antigens were included in the trial and that the --

for the first four vaccines, the antigen content of the medium and low doses or one-third and one-tenth of the full strength dose.

For the Connaught vaccine, only the PT content varied from a high of 5 to a low of 1 microgram. The aluminum content of all vaccines was similar and all doses.

The clinical protocol is outlined in this slide. Briefly, subjects were given a single dose of vaccine or placebo into the deltoid muscle on day 0. A daily log of oral temperature, symptoms and injection site times was maintained during the first week.

For weeks 2 through 4, a second diary was provided to record only abnormal symptoms or signs which occurred. All subjects were examined in the clinic on days 2, 7, 14 and 28 after inoculation. Blood samples were collected for antibody assays before and one month and one year after inoculation for antibody assays.

Four hundred and eighty-one subjects were entered into the trial, approximately 30 per dose group. No severe reactions requiring hospitalization or resulting in permanent disability occurred during the trial. Two subjects experienced fever associated with large local reactions between days 6 and 8 after vaccination; one given

a medium dose of Massachusetts vaccine and one given the high dose of Connaught vaccine.

Prolonged arm pain was seen in one subject given the Amvax vaccine low dose and one given the high dose of Connaught vaccine. Transient arthralgias without objective arthritis occurred in six subjects and were unrelated to dose and occurred in four different vaccine groups.

Hives occurred in several subjects, one given SKB vaccine; although one had a history of idiopathic urticaria. A allergic reaction to guinea pigs associated with wheezing and generalized urticaria occurred on day 1 in a subject given Biocine vaccine. This subject had a known allergy to guinea pigs and was exposed.

The frequencies of systemic symptoms did not differ significantly among subjects given the highest doses of the vaccines. The proportion of subjects reporting pain or tenderness during the week after inoculation are shown here. Discomfort at the injection site was seen in the majority of subjects given vaccine and in most cases was mild.

Frequencies of injection site discomfort in subjects given the top or reference doses of vaccine did not differ significantly among the groups. In addition,

there was no significant dose response for the occurrence of pain or tenderness during the first week in any vaccine group, although it was of borderline significance for the Amvax vaccine.

Up to 22 percent of subjects in each vaccine group developed objective signs of inflammation at the injection site during the first week. Frequencies did not differ significantly among groups receiving the highest dose of vaccine. Large, local reactions, that is, greater than 2,500 millimeters squared, were seen in recipients of all but the Amvax vaccine, but were infrequent and not clearly dose-related.

For the SKB vaccine, there was a trend toward increasing frequency of local reactions with increasing dose of borderline significance. Up to 22 percent of subjects reported injection site discomfort after the first week, occasionally associated with objective signs.

Although the differences between groups were not significant, the occurrence of reactions in weeks 2 to 4 was significantly dose-related for the SKB vaccine. The proportion of subjects given the reference dose of vaccine with onset of symptoms or signs after day 3 were those with biphasic reactions, ranged from 3 percent in the Amvax

group to 28 percent in the Connaught group.

In an attempt to elucidate a potential mechanism for the occurrence of these late onset or biphasic reactions, which have been observed previously upon administration of acellular vaccines to adults, we analyzed the relationship of both pre and post-immunization antibody levels to vaccine components. The occurrence of any redness or swelling was significantly associated with post-immunization level of antibody against the FHA and against pertactin was of borderline significance for serum antibody.

The occurrence of late onset or biphasic reactions associated was associated with higher post-immunization levels of antibody to FHA and serum antigens.

This slide summarized the mean titers elicited by the doses of vaccine. A is Amvax, M, Mass, B, Biocine, SKB, C, Connaught and P, placebo. This is true for the remainder of slides that are shown in this format.

The antibody assay that was performed in Dr. Edwards' laboratory was an ELISA assay using a reference line method and these data show ELISA antibody levels at one month after immunization. Once again, the top dose is the reference dose and for the first four vaccines. The

other two doses are one-third and one-tenth of that level.

For the Connaught vaccine, only the PT level varied. As you will see as go along, that there is lack of dose response for this reason.

For geometric mean antibody levels, significant dose responses were observed in all vaccine groups with increasing dose or with decreasing dose, as you will. There was no significant increase in the level of antibody against any of the vaccine antigens tested in the placebo group and, in addition, the pre-immunization levels against each of the vaccine antigens was similar for all vaccine groups.

Not shown on the slide but in the handout is the fact that for Amvax and Connaught vaccines, there was a statistically significant dose response in the frequency of serum antibody responses from the low to the high dose.

The FHA antibody responses, I will remind you that the Amvax vaccine was formulated to contain PT antigen only. Nevertheless, for geometric mean levels of ELISA antibody there was a significant dose response for the occurrence -- for a geometric mean level of antibody for all vaccines, except for the Connaught vaccine, which had a fixed content of FHA in the high, medium and low doses.

For serum antibody response frequencies, once again, Amvax vaccine and Massachusetts vaccine shows statistically significant dose responses for antibody levels. Significant response to pertactin occurred only in vaccines which were formulated to contain pertactin and for both the SKB and Biocine vaccines, there was significant dose responses and antibody levels and there was a significant dose response for the Biocine vaccine with regard to frequency of significant rise.

Finally, significant responses to FIM antigen were observed in Massachusetts, SKB, Connaught, the high dose of Amvax and the medium and high doses of Biocine vaccines.

Once again I will remind you that the only vaccine formulated to contain FIM antigen was the Connaught vaccine. For geometric mean level of antibody there was a significant dose response for the SKB and Massachusetts vaccine. And for frequency of significant rise to the antigen, Massachusetts and SKB demonstrated a dose response.

We had some interest in ascertaining the persistence of antibodies at one year after immunization and rather than show you all slides, I will show here a

representative slide demonstrating the rather rapid decline of antibody from the one month level to the level observed at one year.

As a generalization, I would say that at one year -- and this is true for all four vaccine antigens -- 20 to 40 percent of the antibody present at one month was remaining at one year.

We had an interest in exploring various factors, which might determine antibody levels and antibody responses to these various antigens. Not shown on the slide is the observation that dose has a significant effect. In addition, we observed that age had a significant effect on preexisting antibody levels to all four antigens.

Shown in this slide is the pre-immunization level of pertactin antibody with age and we found that levels of PT antibody, FHA antibody and pertactin antibody decreased with increasing age.

In contrast this was not affirmed in FIM where antibody levels tended to increase with increasing age with a fairly high level of statistical significance.

Pre-pertactin levels were observed to be significantly lower in blacks when compared with

caucasians. Post-immunization PT antibody levels were significantly higher in blacks, once again, when compared with caucasians. This has been observed previously in infant studies of acellular pertussis vaccines.

The likelihood of a significant antibody response to all antigens was dependent on the immunization level of antibodies, such that the higher level of pre-immunization antibody, the less likely one was to experience a rise in antibody.

The source of antigen was also a significant component of the antibody response and what I have done here, rather than plot in low, medium and high doses, recognizing that these contain different amounts of antigen for the given vaccines, is plot the response against the microgram of that particular antigen that was administered. This effect was most pronounced for the PT antibody responses where you will see that the Biocine vaccine was most efficient, if you will, at eliciting the ELISA antibody levels that we were measuring, followed by Massachusetts vaccine, SKB and Amvax vaccines and Connaught Laboratories.

So, there is a significant effect, which has been observed previously in infant trials of acellular vaccines

and which has been demonstrated experimentally by Ipson inactivating toxoids, using different methods.

So, in summary, all vaccines and doses were well-tolerated. Late onset and biphasic reactions were observed after receipt of all vaccines, suggesting that this is not due to reversion of pertussis toxin. In addition, it is not due to subcutaneous administration because these vaccines were given intramuscularly. And we have generated data to suggest that there may be a relationship to how vigorous the immune response is to the vaccine.

Parenthetically, late reaction occurring between days 5 and 7 were reported by Pappenheimer(?) in his studies of diphtheria toxoid and he hypothesized that these were arthus(?) reactions.

Dose-related increases in serum antibody levels against known vaccine antigens were seen in all vaccine groups and significant antibody responses against antigens not known or formulated to be present in the vaccine were absorbed by immunization with several of these vaccines.

I conclude in my and my co-investigators conclude that expanded studies are necessary to define more completely the safety profile of these vaccines when administered to adults. And that prospective studies

designed to assess the impact of pertussis in adults are indicated in order to define the need for booster immunization in this age group.

Finally, I would like to acknowledge the collaboration of the manufacturers, my colleagues at the NIAID and at Technical Resources International.

DR. FERRIERI: Thank you very much, Dr. Keitel.

We can have questions for Dr. Keitel at this time from the committee.

Dr. Fleming.

DR. FLEMING: Could we go back to your slide that showed PT antibody responses? And while we are recovering that -- that was midway in your talk -- could you clarify while you are going back to that slide what you have in mind when you were saying additional studies would be advised? Did you have specific recommendations for what those studies would be able to assess?

DR. KEITEL: Of the safety profile?

DR. FLEMING: No. Your first conclusion was there should be additional safety data and I think you had a second conclusion that there should be additional data, which I understood to either mean looking at immunogenicity or efficacy.

DR. KEITEL: Oh, my belief is that at this point in time one of the most important studies to conduct is a prospective study looking for bacteriologic evidence of pertussis infection in adolescents and adults so that we can define the need or lack thereof for booster immunization or routine booster immunization of adults.

This wouldn't necessarily solve specific problems such as outbreak control and identified high risk persons, such as health care workers and people with underlying pulmonary disease, but if we are going to contemplate routine booster immunization incorporating these possibly into an adult, DTaP vaccine, I think we need to have stronger evidence for impact of pertussis in these populations.

DR. FLEMING: If I could turn to this slide, if I am recollecting these vaccines correctly, the Amvax, the Massachusetts, the Biocine, SmithKline and Connaught, I believe, on the left, the Amvax was reported earlier today to have 71 percent efficacy after the fourth dose. I don't remember if we had the Massachusetts, but the Biocine, I think, was the 1992 Italy study, 84 percent; SmithKline, the 1992 Italy study, 85 percent and the Connaught, 1992 Sweden study, 85 percent. i believe that is correct.

So, it is just interesting to look at the correlation between PT antibody responses and controlled trials showing efficacy; 71 percent on the left, 85 percent on each of the three on the right. Then if we -- just to finish this off -- we jump ahead two slides -- can we just ahead to the FHA -- the FHA, the latter three on the right would be each 85 percent efficacy. If we could jump ahead to the PRN, one more time, two slides ahead. There it is. Those three are also all 85 percent efficacy. Am I correct?

DR. KEITEL: I don't remember the point estimates of efficacy, but I think the caveat here is that the doses of antigens administered, number one, were not necessarily the same as the separate --

DR. FLEMING: Understood.

DR. KEITEL: -- of vaccine administered.

And number two, I think it is interesting and worthwhile to look at antibody responses elicited by these vaccines in adults. When you look at these levels and compare them with the levels elicited in some of the infant trials, the adults are -- their levels are at least several times higher than those that are elicited in the infants if not many times. So, it is hard to --

DR. FLEMING: Understood, but where I am headed here is one of the questions we will have to answer in the future is if we do studies in adults and can, in fact, identify levels of FHA and PT and PRN, can we use those levels in adults, which is the kind of data you are presenting here, to say something reliable about relative efficacies in adults.

What we will have are the -- what we have, of course, are substantial studies in children that are giving those percentages that I have just indicated. So, you are exactly right, that these don't represent the same doses and antigens and regimens, et cetera, and that adults are different from children.

I am just trying to probe here a bit about how -- what we might be able to see in adults relative to what we are actually seeing in children to get a sense of whether we can get some reliable correlates.

DR. KEITEL: I recognize that there is a general consensus that multi-component vaccines are superior to two and one component vaccines, although the bottom line is that the most rigid interpretation would lead you to conclude that you cannot directly compare trials done at different times under different epidemiologic circumstances

in different countries in different populations.

So that if you don't start with the premise that, okay, this one was better than that one, then you are still left with this horrible situation of not having not only a correlate of immunity, but not knowing what determinants of immunity are.

So, I recognize that we have shown -- what we do know, and I think everybody would agree upon, is that the vaccine confers protection against pertussis and how it does this is not clearly understood. So that our strongest argument at this point would be that since the vaccines are efficacious in infants, there is no a priori immunologic reason why they should not be protective when administered to adults.

That is a simplistic way of looking at it. On the other hand, I think everybody here would feel reassured, greatly reassured, to demonstrate efficacy in adults and I think that is one of the main goals of the adult trial. In the event that that is achievable, recognizing the high variability in reporting incidence rates of pertussis, if it is achievable in this trial, then we may actually come up with bona fide correlates of immunity because the trial design would permit prospective

sampling for antibody levels at the time of illness onset and during convalescence.

So, I guess, I am concerned about overinterpreting serologic data at this point and I am also concerned that it is going to be very complicated because of the heterogeneity of the vaccines which we are reviewing.

DR. FERRIERI: Dr. Keitel, could you comment on your third point in your summary, where you observed "significant" antibody response to antigens not in the vaccines administered, in several of the vaccines, so that you are implying that they were boosted by exposure in nature to wild strains?

DR. KEITEL: No. Actually, that would be one hypothesis to test. If they responded to an antigen that wasn't supposed to be in the vaccine, then what could have happened? Well, maybe they were boosted by natural exposure or maybe the vaccine contained something that it wasn't formulated to contain. I think within the limits of purity that have been established and would be reasonable for the manufacturers, that you could -- let me give one example.

FHA was not formulated to be contained in the

Amvax vaccine. Nevertheless, what you did not see on the slides but which I provided you with in the handout, 40 percent of subjects given the top dose of Amvax vaccine developed at least a fourfold rise in antibody. What you did see was that the mean titer against FHA in that vaccine group, in that group of low, medium, high, given Amvax vaccine rose threefold, 20 in the low to 60 in the high -- 63 in the high dose group.

Now, we know that -- let me take a real low one-- that if you give .75 -- okay, 1 microgram -- let me see -- in FHA, .3 micrograms in the Massachusetts vaccine low dose of FHA, the top dose was 3 and there was a tenfold ranging of dose, down to .3 micrograms that 65 percent of adults, given .3 micrograms, formulated to be in the vaccine responded and their mean titer went from a pre-level of 22 to a post-level of 123, which led me to conclude that FHA is similar in terms of its efficiency, which I have shown-- and I did not show you the slide, but it basically has the same curve. It is not offset like this PT is -- that if Amvax had a .2 microgram contamination, it still would be well above a 99 percent purity for that antigen.

So, you can go through that kind of logic and surmise that tiny bits of antigen that might be stuck on

for whatever reason -- according to George Sieber(?), it is pretty well-recognized that FHA can contaminate in minute quantities the -- excuse me -- the FIM can contaminate in minute quantities the FHA antigen.

So, hence, we saw some 44 percent of subjects getting Massachusetts vaccine, having a serologic response to FIM, which wasn't formulated to contain the vaccine. So, it is not -- I don't think it is terribly surprising. I think what it does is it makes you want to stop and say I wonder what it means. Does this in some way contribute to the efficacy of the vaccine?

You know, I couldn't answer that question. I would be happy to see if anybody has an opinion.

DR. FERRIERI: We have other questions from the table. First, Dr. Apicella and then Dr. Greenberg, if you still have your question.

DR. APICELLA: Wendy, if you look at the PT antibody decline, you presented the high dose on the slide. What happens with the low dose? What does that fall down to? Does that fall to the placebo level?

DR. KEITEL: No.

DR. APICELLA: If you put PT in?

DR. KEITEL: In general, rather than carrying all

these different families of curves, because so many observations were made -- in general, the slope of the curve depended on the peak antibody level. So, it is a steeper slope if the antibody level is high, and that for all vaccines that were formulated to contain the antigen that is in question for all dose levels, the amount persisting in serum was still significantly higher at one year than was seen pre-immunization. And you see the magnitude of that effect.

It ranges for vaccines from anywhere from 2 to 20 or 30 fold persists at one year after immunization.

DR. FERRIERI: Other questions?

Dr. Eickhoff.

DR. EICKHOFF: Dr. Keitel, could you clarify once more, please, the high dose? Was that, in fact, a standard pediatric dose used?

DR. KEITEL: For a couple of vaccines, it was. For others, manufacturers had various formulations and this was the formulation offered for evaluation in the trial.

I guess at this point, two of the manufacturers are going with lower than so-called reference dose as a target formulation for adult and adolescent reimmunization.

DR. FERRIERI: Thank you, Dr. Keitel.

I am afraid we are going to have to take a very brief break and then come back. And I would admonish the members of the committee that if we don't stay focused and we lose any members sitting at the table, we will lose a quorum and we will not be able to fulfill our obligations today. So, let that influence us as the afternoon progresses.

We will take a ten minute break, be back here at 3:17, please.

[Brief recess.]

DR. FERRIERI: If we could all gather and sit down now, this would help us move the program forward. Thank you.

One of the issues that continues to arise is the difficulties of making a diagnosis of pertussis and in my microbiologic circles, as well as clinical infectious diseases circles, we talk about the inadequacies of culture, where we have recent studies where if you don't incubate your plates long enough to 10 or 12 days that you may under-diagnose pertussis by 33 percent.

So, there is more and more emphasis on the use of PCR, but to date there are very few laboratories that offer this as a clinical service and we know there are some

pitfalls involved in the use of PCR.

I would like to call upon Dr. Kathy Edwards to make a statement or two about her understanding and familiarity with the pluses and minuses of PCR for b pertussis.

Kathy, would you mind?

DR. EDWARDS: Well, I think that perhaps the most that I personally learned about the role of culture in PCR is from the studies that are being done in Minnesota, where we are closely following people as they begin to cough. I think for many clinicians, particularly those who take care of adults, not us pediatricians, they don't really think about pertussis until it is too late to actually make the diagnosis.

But what we are finding in Minnesota is that if you do a culture, a bacterial culture, within the first week of the coughing illness, that we are getting culture positivity. We are also finding during that time that the antibody to PT and FHA is still low. It has not gone up, so that, indeed, you can see a fourfold rise if you get the titer very early.

We are also seeing in that study that the PCR, which is being done both in Minnesota, but also at the CDC,

that we are picking up with PCR cases in the second week that no longer are culture positive. So, it really is enhancing our role to diagnose it in the second week.

But, in general, after the third or fourth week, neither are being very helpful and the serology that we have at that time if the acute is obtained at the end of the second week, the third or the fourth week, in general, that is tending to already be elevated so that if you are going to define as a fourfold rise, you won't see that.

So, I think that the NIH study, the NIAID study, by very closely following and using PCR in culture may actually be very helpful in that and I think the Minnesota study suggests that in that second week, the PCR may add more than you are getting with culture.

DR. FERRIERI: Mike.

DR. APICELLA: Kathy, can you distinguish Bordetella bronchoseptica from Bordetella pertussis with the PCR?

DR. EDWARDS: Depending upon the probes that you use, you can. Certainly if you use the PT probe, you can separate in that particular way.

DR. FERRIERI: Thank you, Kathy.

We will move on to the manufacturers' statements.

I have some time limits that were given to me by Dr. Burns. So, we will try to stick to them so that we can deal effectively with the questions we need to address for the Agency.

We will start with the Amvax presentation by Dr. Jo White. And I believe you have ten minutes, Dr. White.

Don't feel under too much pressure. We are only going to press the button --

Agenda Item: Statements from Manufacturers -- Amvax

DR. WHITE: Thank you very much for allowing me to have ten minutes to speak. I am going to have seven overheads and cover three things.

One is that we had a consultants meeting on May 4th. In coincidence with the SPR meetings, we had a lot of pediatricians in town and we actually captured a couple of internists to come and talk about questions that I will show on the -- I don't want the next slide yet, but then what I will do is talk about some of the recommendations or the issues that were discussed with a group that you will see was so big, we didn't get consensus on everything. But I will try to cover points they brought up.

Then I will talk about after we got back to the

ranch, how we looked at what the precedence is, of what other studies have been done looking at vaccines given in adults, where efficacy trials may have been done in other populations.

Finally, I will give you NAVA's(?) recommendation of what we think ought to be recommended.

This is a list of the people that we invited to come and, as you can see here, it was a group of people who are pertussis experts; also, individuals who would be interested in doing clinical studies with us and also some collaborators that we have from Ross Labs.

When the meeting opened, these were the questions I put up for discussion. The first one was based on data from the NIH Phase 2 studies, which you just saw presented by Wendy Keitel. What dose would you use in adults and adolescents? Do you think safety and immunogenicity would be sufficient for a claim for use?

If an efficacy study should be performed, what population would you suggest for this study? What is the attack rate of pertussis in that population? What is the consensus of a definition of a case? And my favorite topic, are challenge studies of pertussis feasible and can this replace an efficacy study?

As I said, with a group as large as we had, I, obviously, did not get consensus. So, I am going to just try to summarize what I heard from the study and there are -- some people in the room if you disagree feel free to stand up after my ten minutes are up.

DR. FERRIERI: Perhaps not.

DR. WHITE: I have to defer to the chairwoman.

Interestingly, over the whole four hours, I think nobody voiced an opinion that they didn't think the vaccine would work or be harmful in any way. That was an interesting observation.

However, because of the way the questions were posed and the way the meeting was conducted, most felt that an efficacy study would be of value in the following: providing epidemiological data -- and I think we have talked about that previously -- also, to help ensure recommendations for universal immunization from such bodies as the ACIP, the AAP and the ACP, and finally, providing cost benefit analysis, which are important for universal immunization.

Eric Hewlett has a great story about challenge studies done at the turn of the century and he could probably entertain you at dinner tonight about that story,

but at this time we don't think they are feasible and due to the lack of standardized challenge dose, long incubation period and the possibility of getting severe disease in the volunteers.

Other issues that were covered, when we got to talk about efficacy studies, as you saw this morning or earlier this afternoon, the attack rates vary dramatically and depending upon which populations you are looking at and how you define the case and how compliant they are, from less than 1 percent to 25 percent. Case ascertainment may be difficult.

As many of you have -- if any of you have done studies in adults, they are less compliant than two month olds and they don't really want to do nasopharyngeal swabs. There were actually a couple of people in the meeting that had done studies in their own institutions, where they were recruiting people for epidemiological studies in their own hospital or HMO and they actually thought people did not come in because they did not want to get a nasopharyngeal swab.

However, with PCR and some nasal washes, you may get around that problem. Correct timing of serology samples, Kathy just addressed that. It was the feeling of

most consultants that anti-PT and anti-fimbrial antigens were the most predictable for disease, not FHA because of the very reasons of cross reactivity. And there are multiple causes of chronic cough in adolescents and adults.

And most thought that CDC case surveillance of pertussis would be the best way to assess if actually vaccinating adults had any impact, of decreasing the overall pertussis load.

The next slide is food for thought for this committee since I know that you are being asked a question in a different sort of way. There have been examples of vaccines licensed for use in the adult population, where efficacy studies were not done in adults. I have those listed on this slide.

I don't dare talk about correlates of -- was it disease risk that we like to talk about now because I think if we took everyone of these vaccines and put it into this committee, that we probably would have very few correlates of disease risk.

Having said that, if you look at hepatitis B -- and the efficacy study was done in neonates, actually born of hepatitis B antigen positive mothers, to obtain a license. Initially, it was licensed for use in high risk

adults and later with healthy infants.

I believe the efficacy study was only done with the Merck vaccine and the other vaccines were licensed based on immune equivalence and also similar manufacturing capability -- similar manufacturing of the vaccine.

For hepatitis A, it is now recommended for adult travelers with the two efficacy studies that were done, one by Merck, one by SmithKline, were both done in individuals 2 to 16 years of age, the one in Monroe(?) and 1 to 16 years of age, the one in Thailand.

The pneumococcal vaccines, which is now recommended for the elderly and high risk -- and some people are getting it younger now since we have so many resistant pneumococci -- the efficacy study was done in healthy young adults in South Africa in the gold miners. And they were actually given a 6 and a 12 valent vaccine, not the 23 valent.

Influenza vaccine, the efficacy studies initially were done in healthy adults, but it was recommended for elderly and high risk. Elderly studies were done later. These were case controlled studies.

Td(?) booster is recommended for adolescents and adults. If you look at the history of that, that licensure

is based on immunogenicity and that was decided on by a group of people that got together to talk about what should be accepted for efficacy in this vaccine. That is listed in the Federal Register at 12-13-85.

More recently, measles-containing vaccine booster doses are recommended based on the epidemiological data and immunological data in adolescents and adults and it is now -- there were no efficacy studies done to show that this decreased the disease in that population, but it is now recommended for the people in the column on the left.

So, taking all this into consideration, NAVA proposes that safety and immunogenicity studies for the DTaP booster dose in adolescents and adults, followed by postmarketing surveillance to evaluate the effect on the epidemiology of pertussis in the United States.

Thank you.

DR. FERRIERI: Thank you, Dr. White.

We have time or we will create time for a brief question or so for Dr. White.

Dr. Keitel, there is a place at the table for you and that legitimizes you in your ability to ask questions. Please join us and then you -- and Dr. David Klein, I don't see you at the moment, but we have a place at the table

with your name so everyone will know you, if they don't. Please join us.

If you could stay a moment there, Dr. White.

Wendy, you had a question for Dr. White.

DR. KEITEL: The question I have relates to the list of vaccines for which the efficacy trial was conducted in a population other than that for which it ultimately was recommended.

Now, I look down the list and I think for most of those diseases or vaccines, depending on your point of view, there is a generally well-accepted correlate of protective immunity so that it wasn't too much of a stretch to say that if you could elicit these immune responses, then you were likely to confer protection against that particular infectious disease.

I am not an expert on all those diseases, but it looks like for most of them, there is a good correlate that in many cases could go so far as to be what we would consider an actual determinant of protective immunity to those infections.

As far as I can tell, that same type of circumstance has not fallen out for the acellular vaccines. I just wondered if you wanted to comment about that.

DR. WHITE: Yes, I would love to comment.

I think if you look at the data that -- in my opinion, I don't think you have good correlates of protection unless you have vaccine failures. If you look at the hepatitis B studies, they were so effective that in people they actually didn't have any -- very few vaccine failures in some of the earlier efficacy studies.

If you follow these people along and look for subclinical infection in endemic area, they, indeed, do get infected even though they have been shown to seroconvert, even though they don't develop chronic infection.

I believe the ten international units per mL was decided on by a combination of the titers achieved in the efficacy study, as well as some animal data. There are also other instances, where influenza, titers to influenza -- even though you seroconvert or have titers doesn't mean you are a hundred percent protected.

I would question -- I could go down a whole list of them and I offer to the committee, if you brought up a lot of these and evaluate them with the same scrutiny as we do others, that some of them may not be as good as others. There are some up here that have fairly good correlates of efficacy. But even measles -- and the CDC showed this.

They thought at first that seroconversion by HI(?) was protective. But in a nice study done by the CDC in a group of college students, who had an outbreak after a blood draw, showed that even though they had antibody, they still got measles.

So, they had to use a higher cutoff. So, these things are being reevaluated all the time and, like I said, you have to have vaccine failures to decide.

DR. FERRIERI: Dr. Klein.

DR. KLEIN: Yes. If you want to stay within the same genus and talk about vaccines licensed without going through the procedure of doing efficacy trials, I guess the best example is the licensure of acellular pertussis vaccines in the 18 month old and four to six year olds, where the data that was used to license that product was based on infant data.

DR. FERRIERI: Thank you.

We will move on now to the presentation from SmithKline Beecham by Dr. Barbara Howell. And you also have ten minutes, Dr. Howell.

Agenda Item: Statements from Manufacturers -- SmithKline Beecham

DR. HOWELL: Thank you.

Also, I have eight slides and this will take approximately seven minutes.

DR. FERRIERI: We are very grateful.

DR. HOWELL: So, you have heard bits and pieces about this trial already and what I would like to do is tell you a little bit more about the details of the design of the study as was requested earlier.

The title, the protocol title, is "A Prospective Randomized Double Blind Trial to Evaluate Acellular Pertussis Vaccine Efficacy in Adolescents and Adults and to Characterize the Epidemiology and Clinical Spectrum of Pertussis Infection and Disease." So, you can see from the title that the study objectives do extend beyond vaccine efficacy into epidemiology.

I just want to first mention that the study was conceived and designed by a group of individuals, including David Klein and Gina Rabinowitz(?) from the NIH. Joel Ward from UCLA's Center for Vaccine Research, is the chairman of the steering committee for the study and there is a group of vaccine treatment and evaluation units and other contract institutions, which are participated, which number in eight and are listed on the slide.

So, the specific study objectives are to evaluate

the protective efficacy of SmithKline Beecham's three component acellular pertussis vaccine in the adolescent and adult population through comparisons of the incidence of infection and illness in subjects who are randomized to receive vaccine or control.

Secondly, to characterize the spectrum of cough illnesses caused by Bordetella pertussis, again in adolescents and adults, and this is through clinical microbiological and serologic evaluation.

Thirdly, to determine the incidence of Bordetella pertussis infections through the same evaluations. Also, of course, to evaluate the safety of the SmithKline Beecham acellular pertussis vaccine, again, relative to randomized, blinded individuals, who receive the hepatitis A vaccine, and to evaluate the serologic response and, as was mentioned, really short term duration of protection to each of the acellular pertussis components of vaccinees.

The study will be prospective, double blind and randomized and controlled and subjects will be recruited primarily from schools and places of employment. This will include hospitals and medical facilities. Really, the goal of the study is to obtain a study population that is representative of the U.S. population in general, providing

some diversity with regard to age, socioeconomic status and ethnicity.

Subjects will be approximately 2,000 healthy adolescents and adults, 15 to 65 years of age, will be randomized to receive a single dose of either the SmithKline Beecham adult formulation PA vaccine or our hepatitis A vaccine. Adverse events will be monitored via diary cards for 14 days post-vaccination. And then active monitoring will be done for respiratory illness via telephone calls made by study personnel every other week.

This is the composition of what I am calling our adult formulation PA. It contains pertussis toxoid, 8 micrograms, FHA, 8 micrograms and pertactin, 2 1/2 micrograms adjuvated to aluminum salts. This is basically the medium dose that was shown to you, the data from the Keitel study, the study that you just saw.

It is approximately one-third the dose of our pediatric acellular pertussis vaccine. This is an overview of the study procedures. As I had mentioned, the subjects will be vaccinated upon enrollment with either a single dose of acellular pertussis or hepatitis A vaccine. Blood specimens will be drawn prior to vaccination, one month after vaccination and one year post-vaccination.

And in addition, in a 10 percent subset, the initial 10 percent who enroll into the trial, blood specimens will be drawn at 6 and 18 months of age in order to evaluate antibody to K(?).

Intensive follow-up will be done, as I said, in the first 14 days post-vaccination with diary cards and study personnel will call twice in the first two weeks to check on the status of the individuals and to make sure they are filling out their diary cards. And, in addition, there will be some blood draws for illness visits. These will basically be done when subjects are asked to report on the occurrence of any respiratory symptoms or non-improving cough of five days or greater duration.

In addition to asking the subjects to passively report this, study personnel will actively call every other week in order to make sure that the individuals are reporting.

When a respiratory illness involving a non-improving cough of five days or greater duration occurs, subjects will be asked to come in for an illness visit and this will consist of a medical assessment, collection of a acute phase serum and collection of nasopharyngeal aspirate to be run for both culture and PCR. Then they will be

asked to return within four weeks for a convalescent phase specimen.

It is actually in the protocol that subjects should be evaluated within 14 days of illness onset and the reason was given by Kathy Edwards earlier.

This is a primary case definition for the study. A case will be defined as any non-improving cough illness of five days or greater duration, evaluated within 14 days of illness onset with a positive culture or a positive PCR or a significant antibody rise to either IgG or IgA in two or more relevant pertussis antigens.

And only illnesses with cough onset, 28 days or more post-vaccination, will be included in the primary case analysis. Of course, there will be multiple secondary case definitions as well.

Vaccine efficacy analysis will be performed in order to assess the relative protective efficacy of the acellular pertussis vaccine and these were the assumptions used in generating the sample size.

Enrollment period for the study will be six months. Disease surveillance, this would be for each subject, should be at least 12 months. For some individuals, it may be as long as 18 months and the mean

will be probably around 15 months.

Loss to follow-up should not exceed 1 percent. The attack rate in the hepatitis A vaccinated group, the control group, is expected to be three per hundred subjects per year and with an assumed true vaccine efficacy of 70 percent at a two-sided 95 percent confidence interval and limiting the lower bound of the 95 percent confidence interval to 20 percent.

So, I just want to say that we are very happy to be involved with this study and to be working with the NIH again on an acellular pertussis efficacy trial in a different population, which we believe is an unmet medical need at this point and also to say that independent of the assessment of vaccine efficacy that is done in this trial, this will be a very important trial in terms of describing disease burden, disease incidence and risk factors for pertussis in the adolescent and adult population.

I would be happy to answer any questions you may have about the study.

DR. FERRIERI: Thank you, Dr. Howell.

Our purpose today is not to have a long dissection of the NIAID trial that is underway. It is to address the other questions posed by the Agency.

Dr. Broome, did you have your hand up?

DR. BROOME: Could you just give us specifically the basis for the 3 percent estimate of attack rating controls?

DR. HOWELL: I believe that the 3 percent attack rate came from a review of the literature and some of the data that you saw earlier this afternoon, expecting that there is underreporting with pertussis and realizing that we are not really sure what the attack rate is.

I would like to also mention that there is a data and safety monitoring board, who will be evaluating and will know what the attack rate is throughout the trial in order to allow for the possibility of extending the trial, should this be an overestimate, in order to allow for additional person months.

I don't know -- anybody else in the room who was involved in discussions about sample size and what attack rate should be used would like to address that? Wendy?

DR. KEITEL: It is correct that it was based on studies primarily using serologic evidence of infection and an emphasis was in particular put on the possibility that there are very high attack rates, but then recognizing likely that it is considerably lower.

The 3 percent was, I guess, a compromise or it was felt doable with the power of the study and the ability to detect differences between the two groups with the possibility for reducing that to a 1 percent based on the DSMB or DSMC or whatever you want to call it in interim analysis.

DR. FERRIERI: Dr. Glode.

DR. GLODE: I was just wondering about with several of the investigators presumably working in hospitals that see a lot of children -- I am just trying to think about if you were immunizing populations that were health care workers, who worked in hospitals with pediatric populations, that those individuals may have had subclinical or mild disease and, therefore, have antibody. And I believe someone said earlier that the response rate in people with preexisting antibody was lower to the vaccine.

So, it is the population that is getting exposed, but if it is a population that already has subclinical disease and, therefore, higher antibody levels, will it make your vaccine look poor because you will get less response to the vaccine. Didn't someone say there was a correlation between preexisting antibody and poor response

to the vaccine?

DR. KEITEL: I guess my response to that is that if antibody in any way correlates or determines protection from infection, then somebody who has high preexisting levels of antibody shouldn't get infected as frequently as people who have low levels of antibody.

One of the main concerns we have is that once you have vaccinated, you may not be able to detect subsequent antibody rises in people who do become infected with pertussis and that is why a huge emphasis has been put on early assessment of illness for collection of respiratory secretions for culture and PCR because of that potential bias of not being able to show a significant rise in somebody who is vaccinated.

DR. FERRIERI: Thank you, Dr. Keitel and thank you, Dr. Howell.

We will move on to the Chiron presentation by Dr. Joseph Eiden. And for some reason, you are said to have 12 minutes, Dr. Eiden. Two minutes sacrificed by your colleague, Dr. Howell.

Agenda Item: Statements from Manufacturers -- Chiron

DR. EIDEN: I appreciate the generosity.

Thank you very much, Dr. Burns and the committee, for the opportunity to present some of our clinical data from our ongoing program to develop acellular pertussis vaccine to provide booster immunization for adults and adolescents.

For the sake of time, I will skip these two slides and mention that the presentation overview today, we have been requested to provide specifically data on immune responses, on infants who have received Chiron's DTaP vaccine in the Italian efficacy trial and in our U.S. studies, comparing the composition of that vaccine to the composition of our acellular pertussis vaccine for adolescents and adults and to demonstrate the relationship of the serologic responses in those groups.

That is what the remainder of the presentation will do.

I might mention quite briefly -- you have already heard some of the data on our DTaP vaccine, which has a very favorable safety profile in over 28,000 infants enrolled in clinical trials. It is licensed in Italy and distributed there routinely. We have filed a PLA and an ELA with the FDA and those are under review.

Efficacy has been shown in the Italian trial with

very high level protection against pertussis by a variety of disease case definitions. In addition to the extended protection, which we mentioned earlier, there is also evidence of protection against pertussis in the period of incomplete immunization following the first dose. This is a very highly immunogenic vaccine, as demonstrated in this particular slide.

Here, we are focusing on antibody responses in the Italian efficacy trial against the three pertussis antigens that are contained in our DTaP vaccine; PT, FHA, pertactin. Also shown in the lower left quadrant is the antibody response to PT as measured by neutralizing antibody assay in vitro. The other assays are ELISA assays.

For comparison here, we have immune responses to Chiron's DTaP vaccine shown on the left with responses and control groups receiving DT without pertussis antigens and in a control group receiving whole cell pertussis vaccine licensed in the United States and supplied by Connaught for the Italian efficacy trial.

The peak responses in infants are shown in green in each case and this is one month following three doses of DTaP. As you can see, there is also a fairly rapid drop

off in antibody titers by approximately 15 months of age, as shown in orange here. However, of note, two things: Efficacy was maintained during this period and afterwards, despite the drop off in antibody titer and the antibody titer shown in orange at approximately 15 months after the third dose still is approximately as great or greater than that of the licensed whole cell vaccine in this case.

Now, the antigen composition of the DTaP vaccine is demonstrated in the middle column in this particular slide; again, three pertussis antigens, including our unique genetically detoxified pertussis toxin, FHA and pertactin, with aluminum hydroxide adjuvant and diphtheria and tetanus toxoids.

In the following slides, I will be showing you immune responses to our aP vaccine for adolescents and adults, which does not have diphtheria and tetanus toxoids and has a composition still containing antigenically equivalent antigens of PT, FHA and pertactin; the amounts being either as great or somewhat greater than in the pediatric formulation.

Of note, in Dr. Keitel's presentation, our company has changed names. So, the Biocine data you were shown earlier will be in some way related to the Chiron

data you are seeing here.

The other thing to note is this dosage of 5, 5 and 5 is midway between the full dose and the one-third dose that was used in the NIAID study that you heard earlier. So, this is a bit different dose level than what you have previously seen on the data.

Now, I am going to very quickly demonstrate with two types of slides antibody responses comparing infants and adults. The first set of slides will be box plots to show you distribution of the antibody responses in U.S. infants after three doses of DTaP at peak titer, one month after the third dose, compared to the responses in adolescents and adults one month after a single dose of our aP booster vaccine.

I will then follow up with a demonstration of the decay curves over time in the adult populations with GMTs and comparing those to the peak response following three doses of DTaP vaccine in the Italian efficacy trial. Of note, these assays in adults, adolescents and infants are all measured in the same laboratory by the same assays throughout in the remainder of these slides.

These are box plots showing log scale anti-PT neutralizing antibody responses for three different trials.

On the left, responses of U.S. infants in a trial conducted at Kaiser Northern HMO in the middle, is a response from one of our adolescent trials and on the right is a response of adults and another one of the Chiron sponsored trials.

Now, across the x axis,you will also note GMT values, but the red boxes indicate the middle 50th percentile distribution of responses. There is a line across the waist of each box, indicating median response, and the outlier whiskers on the lower part are fifth percentile and the upper part are 95th percentile.

Here you can see on this log scale plot the responses in adolescents and adults, middle and right hand sections, are greater than that seen in the infants receiving three doses of vaccine. looking at the same type of plot, same studies, now we are looking at ELISA anti-PT antibody responses; again, infants on the left, adolescents in the middle, adults on the right, GMTs across the bottom being higher responses in adolescents and adults than infants and the responses, as shown on the box plots, at least as great or greater than that in the infants.

Similar data here demonstrated or displayed in the same manner for responses against FHA. Once again, the response is on a log scale, much higher for adolescents and

adults receiving a single dose than for infants receiving three doses of DTaP at two, four and six months of age.

Lastly, we see the same type of very high response in the adolescent and adult populations to the pertactin component of these vaccines when compared to the infants, the GMTs here across the bottom being several fold greater in the older individuals than in the infants after three doses.

Now, in addition to these distribution plots, we put on this display responses of adolescents in a single trial on the left and adults in a single trial on the right, with decay curves over time from two individual trials. The scale here is no longer a log scale but is a linear scale.

In orange are shown the responses one month after a single dose in yellow, the response as it decays at six months and in blue, response as it decays by twelve months. We do not yet have data available on the adults at twelve months. But the adolescent 12 month data will be in this slide and that subsequently. Here, demonstrated the neutralizing antibody titers in vitro against pertussis toxin with very high first responses.

Although there is decay, it is sustained over

time. The same type of plot now looking at ELISA antibody directed against PT; orange being the peak response at one month. We have added here, however, in the dashed line the GMT that was observed from infants, who participated in the Italian efficacy trial. As you can see here, the response in adolescents at twelve months and adults at six months is as great or greater than the infants at peak following three doses in the Italian efficacy trial.

The response against FHA is also quite excellent with several fold higher than in the Italian efficacy trial with sustained antibody in both adolescent and adult populations. And we also see with pertactin responses, once again, the dash line being the GMT from infants in the Italian efficacy trial, several fold higher responses to a single dose of the acellular pertussis vaccine in adults when compared to three doses in the infants in that study.

Chiron, thus, in summary, we have presented an example of a DTaP vaccine that confers protection against a wide variety of case definitions. The antigens employed in the DTaP vaccine in this trial are qualitatively equivalent to the aP vaccine used in adolescents and adults and the antibody response to a booster dose of aP vaccine after a single injection is greater than or equal to that seen in

the infant response to DTaP vaccine following three doses at two, four and six months of age, as measured in the same lab using the same assays.

We believe these data are similar to those which have previously been provided to support licensure of booster immunizations of pertussis in older children, based upon infant efficacy trials and Chiron believes that a pertussis vaccine, which meets these criteria and which can present a strong clinical database for safety and immunogenicity should be sufficient for licensure of a booster dose in adolescents and adults without additional efficacy studies in those populations.

Thank you very much.

DR. FERRIERI: Thank you, Dr. Eiden.

Are there questions for Dr. Eiden?

Dr. Greenberg.

DR. GREENBERG: Joe, if I understood you correctly, you know have efficacy data quite a ways out from that Italian study.

DR. EIDEN: Yes.

DR. GREENBERG: And the serology now is much lower.

DR. EIDEN: Yes.

DR. GREENBERG: If you drew your lines, you could now redraw those with a new line saying that because the children are just as well protected with -- at least for PT, about a tenth as much --

DR. EIDEN: Oh, it is probably less than a tenth because that was a log scale --

DR. GREENBERG: So, the second part of it is is that lower level still above what the normal adult or adolescent has or is that now less than what you would see in the, quote, unprotected adult or adolescent?

DR. EIDEN: The levels, pre-immunization levels, in adolescents and adults is really very small. It is single digits on these ELISA titers. So, they are very small numbers and they barely show up on --

DR. GREENBERG: From the graphs, it looked like they were on -- it looked like they were relatively close; that is, that -- so, an infant three years after immunization, who is fully protected, still has a lot more antibody than an adolescent does.

DR. EIDEN: I won't say that categorically because I don't have the figures in front of me. That is my memory. And if you remember the decay curve at approximately 15 months after immunization, it was still

higher than what was seen at peak for the licensed whole cell vaccine at one month after three doses. So, it was still elevated. It had just fallen off considerably over that time.

But, you know, if you want, I can try and look up the data quite easily.

DR. FERRIERI: Dr. Broome.

DR. BROOME: I am struck that in considering the adolescent/adult indication, we are asking a slightly different form of efficacy for these vaccines, based on the assumption that we are not just trying to protect the individual vaccinated recipient, but we are trying to stop transmission.

I would ask you and all of the other folks involved with the efficacy trials, obviously, those were primarily designed to look at prevention of episodes of clinical illness. Do we know anything about the efficacy against transmission?

DR. EIDEN: The efficacy trials in which Chiron has participated haven't addressed the issue of transmission. They have been specifically designed to address efficacy of the vaccines.

DR. FERRIERI: Anything else?

Thank you then, Dr. Eiden.

DR. KARZON: Do you plan to follow the antibody levels out further? Because it would be of interest to see when they reach their original baseline or whether the curve flattens out.

DR. EIDEN: It is our intent to continue to follow these until they go down to baseline if that is possible. As you know, it is quite difficult to continue but we would very much like to know when we have reached baseline.

Thank you very much.

DR. FERRIERI: Thank you.

We will move on to the next presentation from Wyeth-Lederle by Dr. Suzanne Lasaque(?). Apologies if I did not pronounce your name correctly.

Agenda Item: Statements from Manufacturers -- Wyeth-Lederle

DR. LASAQUE: I would like to thank the organizers for the chance to present data today.

Today I will be discussing results of two studies done with our acellular pertussis vaccine component in adults; one in the United States and the other in Germany. Hopefully, this presentation will be clearer than that last

view of it.

The first study was performed in collaboration with Lederle and Dr. Edwards. The study was performed at Vanderbilt in adults, 18 years of age and older. In this study, it was a double blind, randomized, placebo control trial; 118 adults were randomized to one of four groups. The first group received the standard adult tetanus diphtheria vaccine and the other three groups were randomized to TD formulated with either full, half or quarter strength acellular pertussis vaccine component.

Local and systemic reactions were assessed by diary for 14 days following vaccination and serum samples were collected for antibody assay before one month and one year after immunization.

I would like to review the formulation of the vaccine. As I mentioned, it contained diphtheria and tetanus toxoids used in our adult TD formulation and, in addition, had 300 hemagglutinin units of acellular pertussis with protein in the following proportions; 86 percent, FHA, 8 percent toxoid, PT, 4 percent pertactin, 2 percent fimbriae 2.

To briefly review the safety data, most of the safety reactions reported in the study concentrated at 24

hours and, in fact, very few reactions were reported after five days. As you will see here, regardless of the concentration of the pertussis component, reactions were mild. The most common was local pain at the injection site and, in fact, all the reactions occurred either equal to or less than what was seen with the TD formulation.

The results of the antibody analysis performed here are IgG assays, two PT, FHA, pertactin and agglutinins. These are results from Dr. Edwards' lab. As you will see for each of the antigens in each of the vaccine groups, there was a statistically significant increase between the pre and the one month post, the dose. There was no response to pertussis antigens among those who received TD and there was no difference in the post levels achieved between the three dose ranges of the acellular component.

Among the subset of individuals who had sera available at one month and one year post the immunization, you will see that there was usually approximately a 50 percent drop from that level achieved one month after the dose.

Moving on to a similar study in adults in Germany, this one, however, used a monovalent, acellular

pertussis vaccine, without diphtheria or tetanus. In this study, it was an open labeled study of a single dose of vaccine. However, in this instance, healthy adults were grouped into two. The first group had received at least three doses of pertussis containing vaccine in childhood. The second had no previous pertussis immunization. Because German records require the keeping of an up-to-date immunization record, we could verify that, in fact, all of these subjects had received at least three doses in childhood.

Again, vaccine safety was assessed by a diary card, in this case for 72 hours post-immunization and serum samples were available immediately pre, seven days, four to six weeks, six months and twelve months post-dose.

Again, you will notice that the acellular pertussis component here is identical to that contained in the vaccine that was tested by Dr. Edwards' group in the same proportion.

Similar to the data that Dr. Edwards has presented, the reactogenicity, which was reported, was mild and, again, the most frequent report was local pain. Local reactions were rare and there were no reports of fever in either group.

In a similar fashion, the immunogenicity as GMTs, antibody to IgG, to each of the antigens contained in the vaccine and, again, regardless of whether they had received prior pertussis vaccine or no previous vaccination, you will see a significant increase for each of the antigens in samples that were taken four to six weeks after the dose.

Another way of showing response, looking at responses greater than or equal to a fourfold rise in titer from the baseline to four to six weeks post, you see in both groups, regardless of the previous history of immunization, there were excellent responses for the first three and less over fimbriae 2, which is contained in much less lower concentration.

At this point, I would like to show data that looks at antibody response, in this case, a pilot study to the German efficacy study, where you will see displayed geometric mean titers for each of these antigens one month after the third dose and one month after the fourth dose. All these assays were performed in the Lederle laboratory. So, I am using these to compare to the results achieved in German adults where the same assays were performed.

What you will see is that in these results in study children where efficacy was demonstrated to be 81

percent, that the adults achieved far greater titers one month post-dose many fold higher than those achieved by the infants where the vaccine was efficacious.

So, in closing, I would like to suggest that based on the efficacy data of acellular in young children, it is clear that a booster dose in adults results in antibody levels to all the antigens that are well above the levels shown to be effective.

Licensure of acellular pertussis as a booster dose in adolescents and adults should be based on this ability to induce an antibody response, which is above those levels shown to be protective in children. I would like to add that certainly as we go forward with further studies, we consider it important to prove the burden of disease of pertussis in adolescents and adults.

If there are any questions, I will be happy to answer them.

DR. FERRIERI: Thank you, Dr. Lasaque.

Questions from the panel?

Dr. Fleming.

DR. FLEMING: Could we see again the reactogenicity data from the first randomized trial with full dose, half, quarter? That went by fairly quickly.

So, essentially, looking at these data, is it correct to interpret that the local reactions and systemic events were somewhat less in the presence of the AC at some dose?

DR. LASAQUE: Yes, that certainly is one interpretation.

DR. FLEMING: And the rationale for that, any thought about that?

DR. LASAQUE: We have thought about it. I would be interested in hearing what Dr. Edwards thinks, as well. We don't have a clear explanation.

DR. EDWARDS: They actually were different lots unfortunately. The big T, little d was a different lot and it was mixed with the acellular dose.

DR. FERRIERI: Yes, Dr. Daum.

DR. DAUM: I have a question and a comment or a request for a comment, I guess.

The question is toward the end of the talk you twice referred to antibody levels that have been shown to be protective. I wonder if that comment is a little bit misleading because there were antibody levels that you measured during an efficacy trial on subjects who were protected.

DR. LASAQUE: Right. I think that would have been -- your choice of wording is perhaps more accurate than the ones I used.

DR. DAUM: Okay. The second thing I would like to hear your comment on that I thought were very interesting that you showed was the data in the German adults and you commented on the post-immunization titers that they had, but I thought they were kind of interesting to look at the pre-immunization titers that they had, comparing people who had received pertussis vaccine with those who had not.

It looked like for some of the antigens, they were almost incredibly the same and for some --

DR. LASAQUE: And for others, they are --

DR. DAUM: -- and I wonder if you did any analysis of those differences and what your conclusions are about that.

DR. LASAQUE: I think that you possibly were referring to some of these, where they are most striking. These were, in fact, different -- the pres were different both for fimbriae and for pertactin among the two groups.

DR. DAUM: And not -- I mean, is that a statistical comment or --

DR. LASAQUE: Yes, but it did not influence where they ended up.

DR. DAUM: Were the differences for PT pre the same and FHA --

DR. LASAQUE: No. Those were not statistically significantly different.

DR. DAUM: Does that imply anything about previous pertussis vaccines received?

DR. LASAQUE: I am not familiar with the formulations of vaccines that were used in Germany during that time. They were whole cell vaccines, obviously, but the components, I am not fully acquainted with.

DR. FERRIERI: Thank you very much.

Please use the microphone, Dr. Paradiza.

DR. PARADIZA: To the issue of correlates of immunity, this morning Bob Colberger presented data that suggested that maybe we are getting towards correlates of immunity with -- showing that the burden of disease was in the children who had the least response to some of the antigens. I think others are working in the same direction.

So, I wouldn't give up on the potential for a correlate for acellular pertussis. That may be vaccine

specific, but that is what we are talking about anyway.

DR. FERRIERI: Thank you, Peter.

DR. FLEMING: Could I follow up on that?

But if it is vaccine specific, then how do we really use it to look at future vaccines in looking at relative effects of various vaccines and how do you explain the Swedish trial results where within the same trial you see strikingly different efficacy, where the antibody levels on PT and FHA went in the opposite direction?

DR. PARADIZA: I said it needs to be vaccine specific only because we have always dealt with vaccine specific. I mean, they are all different and the presumption is or at least mine has been that we would link back to our own efficacy trial data.

You know, the question that you raised earlier, I think, is a good one, but while the antibody to PT and FHA was going down in one vaccine, it also had two other components in it that were probably affecting that efficacy.

So, you would need to look at the responses to those two vaccines individually. I am not implying that you are going to get a correlate that is going to be universal for all vaccines.

DR. FERRIERI: Thank you.

We will move on then to our last presentation from the manufacturers and this is from Connaught Laboratories by Dr. Carleton Mischevitz.

Agenda Item: Statements from Manufacturers -- Connaught Laboratories

DR. MISCHEVITZ: Actually we didn't request time to make a presentation. So, there is no formal presentation that we have. The data that we have is similar to the other manufacturers.

We have done dose ranging studies with both acellular pertussis component alone, as well as with DTaP and those dose-ranging studies did show a dose response to both the PT and the FHA in the vaccine.

We also have taken the opinion that linking the antibody response to the trials where efficacy was shown with our own vaccine would be a proposed mechanism of potential licensure of a product in adults.

So, I would be happy to answer any questions if there are any.

DR. FERRIERI: Committee?

DR. MISCHEVITZ: Okay. Thank you.

DR. FERRIERI: Are you sure you have no

questions? Otherwise, then we will move on back to Dr. Burns and the FDA presentation of questions.

Agenda Item: FDA Presentation of Questions

DR. BURNS: I would like to introduce the questions that we would like the committee to consider. We have two of them.

The first is: Can demonstration of efficacy of a given acellular pertussis vaccine administered as a primary series to infants serve as a basis for efficacy of that vaccine when administered as a booster dose to adolescents and adults?

I would like to emphasize that we are talking about if efficacy of a given vaccine has been demonstrated in infants, can we use that data for that vaccine. We aren't talking about anything else going between vaccines, between two different vaccines.

If the answer to the first question is "yes," then is demonstration of comparable antibody response in adults/adolescents and infants an appropriate indicator that the different age groups respond to the vaccine in equivalent manners.

Well, have we used antibodies to bridge between age groups before? And the answer is "yes." I would like

to just remind you of that here. Demonstration of efficacy of a given acellular pertussis vaccine administered as a primary series has been used as a basis for efficacy of that vaccine when given as a booster dose to older children and antibody responses were used as a measure to ensure that the different age groups respond to the vaccine in equivalent manners.

I would like to just give you three examples and I will go in the order that the vaccines were licensed.

In 1991, ACEL-IMUNE was the first acellular pertussis vaccine licensed in the United States for booster use. The efficacy study was a Japanese household contact study. Three doses were given to two year old children by a reinforcing dose one year later. The licensed indication was for the fourth and/or fifth dose, which could be given to children up to seven years of age.

This was discussed by this committee in January of 1991.

The second example is Tripedia, which was licensed in 1992. The efficacy trial was in Sweden in 1986 and 1987. Two doses were given to infants beginning five to eleven months of age, seven to thirteen weeks apart. The license indication was for the fourth and/or fifth

dose.

Again, this was discussed by this committee in November of 1991.

And the third example is INFANRIX. The efficacy studies were in Italy and Germany. Germany, you haven't heard about today, but you have heard about it before. It was a household contact study. There were three doses -- in both of these trials, three doses were given in infancy. The licensed indication is for the first four doses or for completion of the five dose series after whole cell pertussis vaccine. So, children up to the age -- up to the seventh birthday could get this vaccine.

This was discussed by this committee a year ago.

So, again, I will just --

DR. FLEMING: Before we go on, isn't there one more example? This past October --

DR. BURNS: That is right. The ACEL-IMUNE was licensed for the fifth dose based upon infant efficacy data. But it was already licensed. So, I didn't --

DR. FLEMING: There were actually two that we considered in October. The other one was the Amvax.

DR. BURNS: That is true and your recommendation --

DR. FLEMING: And this committee had serious concerns about safety of the fourth dose and safety and immunogenicity of the fifth dose and specifically raised strong recommendations for gathering additional data to expand the inference from the first three doses beyond that point.

DR. BURNS: Right. I think that -- wasn't that more of a safety question, rather than immunogenicity for the fifth dose?

DR. FERRIERI: Yes, primarily a safety reactogenicity issue, was it not?

DR. FLEMING: In my recollection, it was primarily reactogenicity on the fourth and fifth dose and then also immunogenicity on the fifth dose.

DR. BURNS: They had no data on the fifth dose. So, it wasn't even being considered.

DR. FLEMING: We were asked to consider it.

DR. BURNS: Okay. I am sorry. You were, yes.

So, I will leave the questions up in case you want to refer to them.

DR. FERRIERI: Thank you, Dr. Burns.

Well, we are at this point in time where we can give serious thought to the questions and I would encourage

free discussion by the committee members.

Agenda Item: Committee Discussion

Let's start with the first question. Is there anyone who would like to tackle this from a discussion point of view, raise any particular issues?

Dr. Apicella and then Dr. Clements.

DR. APICELLA: I think the first thing is that we looking at two different diseases in a way. Disease in infants, it has been discussed already, is significantly different than disease in adults. I am not sure you can make a judgment based on the efficacy of the vaccine in infants, to what it will do to the disease in adults.

Plus, the question was raised about the other factor, the effect on colonization in adults. This really hasn't been looked at and would be, I think, a component of efficacy of the vaccine in adults.

DR. FERRIERI: Dr. Clements.

DR. CLEMENTS-MANN: Just for a point of clarification.

On the first question, when you emphasize the word "given acellular pertussis vaccine," I just wanted a clarification whether you are thinking that if it were a lower dose or a higher dose or something like that, would

that be considered the same vaccine?

DR. BURNS: Well, I think that we -- I would like to hear what the committee has to say about that subject because, obviously, some of the manufacturers are considering going to a lower dose. What if you had the scenario of -- you had a lower dose, yet, the immune response that is measured by antibodies was still quite robust as a booster dose in the adults?

DR. FERRIERI: Does that satisfy you?

Dr. Keitel.

DR. KEITEL: I just wanted to add one complication, which is does the fact that the pediatric efficacy trials use DTaP vaccines also complicate the issue? Most of the proposals or many seem to be for acellular pertussis vaccines in adults that may not be formulated to contain adult TD. How does that influence this?

DR. FERRIERI: Drusilla, did you want to respond to that?

DR. BURNS: I think that what we have done in the past with the combination vaccines, we have one acellular pertussis vaccine that was licensed for booster dose in a combination with Haemophilus. And in that case, we used

antibodies as the correlate.

The question is could you do that here. Also, if the antibody response is still very high in adults, much higher than what the infants got, even though in that case, the T and the D was present, would that matter?

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: For clarification, are there any known examples where immunization in children that is effective has been shown to not be effective in older -- I mean, I would like to know that if there are examples of that. Certainly, the converse can be true, where immunization in adults may not be effective in children, but I can't think of a good example. So, I would just like my ID colleagues to --

DR. FERRIERI: Dr. Poland.

DR. POLAND: ETG(?) may be an example. Controversial, but it may be one example.

DR. FERRIERI: Quite a different formulation, as well as disease.

Is there anyone who wants to take up the point raised by Dr. Apicella, though, that he thinks there are very different diseases and --

DR. FLEMING: Before we leave this last point,

just a quick comment. How many settings are there where we have done well-designed, well-conducted efficacy trials, looking directly at effects on reduction in infection rates in both children and adults, because we would need to have an array of those types of settings to be able to draw from those to answer your question?

DR. FERRIERI: Dr. Eric Hewlett.

DR. HEWLETT: I will address the issue of the disease process.

I think that it is probably more a matter of degree than it is significant different processes. We really don't know the mechanisms of this disease and why people cough the way they do. There are a whole lot of things that are being worked on at the present time.

But given that, I think the severity of disease is probably different. In fact, probably is representative of some level of residual immunity, so that there is protection against some component of severity.

As a result -- and you brought up also, I think, the issue of asking for protection against colonization or transmission, as Claire mentioned before. I am not sure that that is fair to hold the vaccine to that standard at the present time. That is an objective that we have and

that will be nice if that happens, but I don't think that that has to be a requirement at this point in order to consider licensing this vaccine for this indication.

Now, there has been mention several times during the course of the discussion, the issue of subclinical infection or colonization. I am not sure exactly what that means, but I think it is a semantic issue. There certainly is evidence that one can be exposed to this organism and be transiently culture positive.

Claire Broome showed this a number of years ago. And then not ever develop symptoms. I think what we are talking about here as subclinical infection is probably someone who is exposed to the organism, whose immune response then rejects that organism in an appropriate fashion. Therefore, they never reach the stage of having clinical disease, but it elicits an immune response, which we see. If you look only -- not in a population of symptomatic individuals, but serologically in a population, you are going to see a higher level. That is why the numbers, Tom, were so much higher if you just look, do a sero survey as opposed to looking at people who are symptomatic.

So, I think it is probably -- the real value is

somewhere in between. As Claire alluded to before, are we close enough to be able to do the NIAID trial? That remains to be determined, but I think it is somewhere below the number that we get on serologic basis, but somewhere above where we have thought it was previously.

DR. FERRIERI: Let's continue that theme.

Claire, would you like to keep it up?

DR. BROOME: Well, I would actually like to just agree with Eric in terms of the implications. My understanding of what this committee -- what the FDA needs to wrestle with is is this efficacious against clinical disease in the vaccinated individuals? But I do -- and I raise the transmission issue more thinking actually for the ACIP's problem of how would you use a licensed product and also just to have people think creatively about what might be done to document impact on transmission.

DR. FERRIERI: Dr. Clements.

DR. CLEMENTS-MANN: Yes. I think the studies to look at transmission and probably causation could better be done in an effectiveness study, you know, where you immunize everyone and then look at the effect in the community or households or what not or high exposure situations.

So, I think there are other ways to address that question once you know that it is immunogenic enough and you have some idea of its effectiveness.

DR. FERRIERI: Dr. Snider and then Dr. Klein.

DR. SNIDER: Well, perhaps this is a little bit redundant, but I think what we are saying is or I think what I would say is that I certainly would be willing to accept the notion that the vaccine would prevent clinical disease in adolescents and adults to the same extent or greater, as it does in infants.

So, if that is the clinical indication for the vaccine, then, you know, I think you have your answer. But what we are struggling with is whether that indication really is what is necessary to determine whether the vaccine will benefit the pertussis situation in this country because we don't know enough about transmission, colonization issues to be able to know whether using it for the indication that we use it in infants will have an impact on the pertussis epidemiology.

My intuition is that it would have some impact, but if it reduces the -- for example, if it reduces the duration of symptoms or the duration of shedding of the organism, certainly if it were shown to reduce that and the

likelihood of colonization, which we can't exclude as being another mechanism that infants get infected, with coughs stimulated by some other way, then we may not have a big impact.

So, we will be left with the dilemma of a licensed vaccine for which we really don't have any recommendations potentially.

DR. FERRIERI: Please, Dr. Burns.

DR. BURNS: I think I want to clarify the question that we need answered today and that would be would the vaccine work in the individual who receives it. Your point is very good. I think it deals more with recommendations for use, which would be other committees.

DR. SNIDER: Thank you for that clarification because I think that helps us focus our answers then.

DR. FERRIERI: That is great, Dixie. I think we do need to keep that in mind.

Again, David Klein and then Bob Daum.

DR. KLEIN: During our discussions for developing our design of the so-called adult pertussis study that we are planning to do, we did discuss the issue or the possibility of looking at secondary attack rates. We thought that was an important issue. Unfortunately, it

just didn't work out because we didn't think there would be enough cases among each of the individual sites to warrant such an approach.

So, we felt that maybe -- I don't think any given site would probably have more than five or six cases of disease. So, it just didn't allow for that type of study.

DR. FERRIERI: Dr. Daum.

DR. DAUM: In terms of trying to come to grips with this myself, three issues seem to be important to me. One is that the antibody data that have been presented by many different people now as potentially helping us to bridge from adult to pediatrics haven't helped me because the correlate isn't there that I would like to have in terms of the trials that were done in Europe particularly between efficacy and the amount of antibody produced.

So, try as I will and staring at the nice slides we saw today, I can't make the leap and I don't understand how to do that interpretation. So, I guess my first problem is is that I can't do the bridge trick and I can't get there from antibody.

DR. FERRIERI: From children to adults.

DR. DAUM: Yes.

The second thing is is that the number of doses

being talked about for an individual is different. We give children three doses as a rule and then most often start measuring efficacy, at least in a serious way, after the three doses and, yet, at least what I think I am hearing is that we are planning a single dose intervention for adults. That, to me, is different.

So, I would say that is an unknown as to whether that would be as good as a series in children.

The third thing that keeps coming back to me -- and I guess maybe reflects some ignorance about what adult pertussis looks like in terms of its spectrum -- is that there is a difference in how the vaccines are performed -- and I think I include the whole cell vaccine here -- in terms of mild disease versus clinically severe disease.

There is no doubt with even the whole cell vaccine that we had good control of clinically severe disease in this country and much less good control of mild disease. I think the acellular trials underscore this even more and we sort of talked about that a little bit earlier this afternoon.

So, my bottom line is I would like to know more about adult pertussis and what it looks like and its manifestations before I would be enthusiastic about going

forward with this kind of extension. And I am looking to the trials that have been talked about today as potentially very, very exciting in supplying that kind of information.

DR. FERRIERI: Dr. Burns, could you respond to Bob's point regarding the single dose, confirming that that is the -- this was puzzling to me as well and I was hoping --

DR. BURNS: I think that it is fair to say that most people who have thought about adult pertussis vaccines are thinking only in the single dose terms. I think everybody is a little bit nervous about the reactions they might get in adults if they got three doses of these things, given what we have seen in kids.

I do have a question, however. We aren't talking about necessarily -- necessarily about naive adults, adults that have never been vaccinated or never seen disease. We are talking more on the lines of a booster dose. In that case, would that change how you think about it in any way, single dose versus the whole series?

DR. DAUM: I don't know the -- I think that is a very intriguing question and I would be the first to say I don't know the answer. That is one of the reasons I wanted to hear more about the German adults that were and were not

naive to previous immunization. It looked like they sort of looked the same with the major antigens before they came to the shot and then they looked the same after.

DR. BURNS: The ones that -- and maybe the people from Wyeth-Lederle can correct me if I am wrong, but in Germany there was a fair amount of disease. So, those adults that were not vaccinated may not be naive adults. They would be exposed to the organism.

DR. FERRIERI: Dr. Hewlett and then we will come back to the other side of the table.

DR. HEWLETT: I think perhaps the issue of antibody and correlate and such can be clarified a little bit by acknowledging that in comparison with this morning, we know a great deal less about this organism and the disease process with regard to protection than we do the Hib disease.

The point is that we have some major dilemmas and I think, Drusilla, you may want to elaborate on this, but the control, testing and regulation of this vaccine at the present time is in a peculiar set of circumstances. The whole cell vaccine was tested at least in part by intracerebral mouse challenge test, protection against that entity and the acellular vaccines, most if not all of them,

don't pass that test as constituted in the past.

As a result, we -- and that test was validated on the basis of the trials that were done in the mid-fifties in Great Britain. So, as a result, there is no mechanism by which to document that the present acellular vaccines are, in fact, to control them, other than the use of immunogenicity.

So, immunogenicity of the acellular vaccines for the components that they contain is the major control mechanism for release of each batch of vaccine at the present time. That is in distinction to the fact that we know that the clinical trials didn't reveal that any of these single antibody measurements correlated with protection.

So, the whole process is a bit awkward at the moment and that is compounded by the fact that at least one of the whole cell vaccines that was available in the United States was passing the mouse intracerebral challenge test and was being released, did less well than expected in the efficacy trials, indicating that that test that we had previously may not have been as good as we thought it was. So, we really -- and there are actually immunogenicity data from that vaccine to suggest that it was, perhaps, less

immunogenic than some of its peers, which gets us back to the point that even though there isn't a serologic correlate, there certainly isn't anything better and there is reason to think that that is a not unreasonable indicator of what is in these vaccines and how reasonable--certainly, how reproducible they are.

So, if we look just at the hard data that we have, we don't know very much and we wouldn't be able to do anything right now. If we take at face value that we are in a bit of a dilemma and look logically at where we are with this vaccine -- and as Eric said, there is not any precedent for the fact that a vaccine that is established to work well in children then doesn't do so or perhaps not in adults, then I think that it is not unreasonable to say that we make a leap forward to do this.

But we certainly can't document it with hard data.

DR. FERRIERI: Dr. Clements and then Dr. Greenberg.

DR. CLEMENTS-MANN: I think that boosting with this vaccine is not unlike boosting with tetanus and diphtheria. I think the single immunization is fine. I think that what may be happening is that as we have

improved our immunization rates and more cohort children have become immunized, is that there is less natural disease overall boosting people every year and that there are susceptible people who only got their -- you know, their distant immunization from the actual immunization. So that it wouldn't surprise me that we don't need to boost people in adulthood.

I think immunogenicity -- showing comparable immunogenicity or better than what was seen in the children who appeared to be protected, is a reasonable bridge and so that is --

DR. GREENBERG: Correct me, but you have already here at this committee established that a single booster dose with these vaccines is licensable or recommended that it was -- I would assume that the committee would want to have consistency in its approach. So, what I am missing here is how -- what would be the difference here versus those prior decisions that would make you feel that this was a different situation?

You have said you could give this dose to a five year old, right, as a booster? And that that is okay? So, now the question is why is a 15 year old, is there a leap that a 15 year old may be different enough from a five year

old that you would do something opposite to what you did a few years ago?

DR. FERRIERI: Would you like to tackle that, Drusilla?

DR. BURNS: Well, I think that is an important point and I would like to hear what the committee has to say on that.

DR. FERRIERI: Well, why don't I just start.

I think that it is just part of the cautious approach we use to introducing a different application for a vaccine. So, there are issues of how they will react, what will be the clinical side effects conceivably and so on. So, I think we are not being inconsistent. We are being super scrupulous in our examination of the issue.

And I think the Agency is prompting that in order to better understand whether we see flaws in this approach than may be apparent.

DR. GREENBERG: I totally agree. The critical thing would be to say what are the differences or were mistakes made previously or was there data that was not understood because you obviously went through a big decision-making. So, best is to use information that you have already developed.

DR. BURNS: I think that one of the -- we have used it to bridge between the very young children and the four to five to six year olds. Now, the question is can you now go up in age?

DR. FERRIERI: Other points from the committee regarding this Question 1?

Dr. Fleming.

DR. FLEMING: And, in fact, even with the age four to five, there has been some recent rethinking on the part of this committee, at least relative to one of the vaccines that we have been looking at. It seems to me to partly get at your question, when I look at Question No. 1, there might be a simplistic way to respond to that question, which is simply if you have a vaccine that has been assessed in infants and if you come up with an efficacy of 70 to 85 percent, which is a range that we have seen in infant trials, can you conclude quite plausibly from that data that there is some level of efficacy in adults?

I actually would be very interested to defer to clinical colleagues on the committee as to whether that answer is "yes" or "no." It is not entirely clear what that answer will be. But I am wondering if we need to

answer a much more difficult question, which, in fact, partly gets at your question about the difference between the fourth dose to a child versus a dose to an adolescent or an adult.

Ultimately, we need to be able to assess risk benefit and when we look at benefit, we are looking at efficacy and a number of issues that I have been hearing through the discussion today that could impact efficacy differently for adults is the different biology in children versus adults, the different dose levels that are being proposed for adults and the different number of doses.

So, there certainly are reasons to anticipate there could be differences. A major and difficult question is can we presume that an efficacy of 70 to 80 percent in children can be assumed to exist in adults? It probably is much more likely and much more readily achieved to conclude that you have something, 20 percent, 30 percent. But I would anticipate it would be much more difficult to justify that it truly is in the order of 70 to 80 percent.

Now, the other part of this issue, though, is risk in risk benefit and understanding reactogenicity in adults is an issue of considerable concern and of particular importance in risk benefit is what is the

overall prevalence of clinically relevant disease.

When we were listening this morning to Dr. Farizo's presentation, it is clear that the answer to that is unclear because we are not talking -- I think Eric was pointing out that we have to be very careful that what we are distinguishing as disease that might exist on the order of 1 to 10 percent may be predominantly subclinical disease or maybe even just an immune response to exposure and not disease at all.

So, it would seem to me that when we are looking at risk benefit in adults, which is different from the childhood setting, we have got to be able to reasonably, effectively understand what this level of risk is. If this level of risk is very low, then reactogenicity becomes a much greater concern if we are not preventing that many cases relative to the number of individuals that have to be exposed or have to be vaccinated.

I know the focus of this discussion isn't the NIAID trial, but a trial such as the NIAID trial may not be necessary to be able to anticipate some level of efficacy in adults, based on efficacy in children. But what it would do is it would be able to much more clearly identify whether that level of efficacy is largely preserved and

importantly it would give us insights on these other two issues. It would give us direct comparative insights on what is the prevalence of disease in this setting, as well as reactogenicity.

If, in fact, the prevalence of disease is closer to one in a thousand rather than thirty in a thousand, as being proposed here, that is an important answer in itself because you may not have enough data to establish what the relative efficacy is, but you do have enough data to challenge whether disease prevalence is of such a level that it would justify an intervention.

DR. FERRIERI: Dr. Karzon.

DR. KARZON: This has been a very interesting discussion. So, I benefit by listening to all the pros and cons here and I have my own pros at the moment.

First, a brief comment about the fact often reiterated that we have no correlates of immunity and that puts the fear of God into most of us who are used to being able, if it is an antibody-driven protective system, to have a level in fluids higher than in measles and so on, but there is a level, sometimes a range of level.

What we haven't done is look upon these five antigens that we are using and there are more if we wanted

to use them, as virulence factors that are co-controlled by the genetic basis of the organism. We are looking at them as singletons when they are not meant to be in nature. What we need to do -- and we were talking about this a moment ago at the break -- a multivariate analysis to see if you can make more head and tails out of the single responses, subtracting the fact that some of these antigens are shared by other bacteria.

But there is no question that making antibody to virulence factors is bound to be useful and it has turned out to be this way.

That next leads me into why we think a single dose in an adult would be functional when it isn't in a child. Well, that is pretty old immunology. These are well-primed people if they have been immunized or had remote infection and they will get a prompt and high response on the subsequent dose. We will run into trouble if we don't get primed people unless some of these cross antigen systems or functions. I don't know that.

But someday we will immunize most of our infants, someday soon, and we will be dealing with primed people.

What is our expectancy for gains in this system? I think they are reasonable, but one couldn't recount them.

It ought to make the disease more modest, if it doesn't do away with it entirely. It should do that and you can expect that. It does in children and I don't know why it would be not so in an adult.

If the disease is more modest, what does that mean? It means that the bacteria ought to be present for a shorter period. The count might well be lower. The rate of coughing and the intensity of coughing might be diminished and all those things are related to transferability of the bug.

So, my expectancy is that it should have on an epidemiological basis an important contribution. It is important to know the duration of even the boosted antibody because we may be in a situation where we are going to have to reimmunize every ten years or something like that. I don't know. I wouldn't worry about that at the moment. That lies for the future.

Reactogenicity has been mentioned and someone asked why we didn't do this with DTP if we thought this was good for adults. Well, there is a big reason and that is the reactogenicity. At least we fear reactogenicity being more severe in adults. When I tried to find this in the literature, it wasn't clear actually. It seems to be

handed down through the generations of pediatricians. I don't know. But you don't immunize a child over seven was the operational rule. And I tried to find a base for that and I wasn't sure I could in the literature anyway.

But at any rate, reactogenicity is something to watch, especially the delay type thing that might occur at five days or beyond that I don't understand, that has been described in Sweden as well with the newer vaccines.

So, my thinking is that we can transfer the presence of the appropriate antibodies as protective in adults and that we should go ahead and use it. Whether we need efficacy trials -- it would be very nice to have efficacy trials without going through the mathematics of -- I would think because of the nature of the population and the numbers, this would be one whale of a difficult thing and especially if you want to find out something about transferability in the same experiment. That is not an easy thing to do. If somebody wants to pay for it and do it, I suppose it would be very nice. I wouldn't stop it, but I don't know that I would go out of my way to get it right now.

I think we will learn the same things without an efficacy trial. We will soon enough find out.

DR. FERRIERI: Thank you, David. I think that you and other committee members have really pointed out the limitations, what we know, what we don't know and that you have now brought us to the point where I think we can address what the Agency would like to know from us. So, I think we have got to cut bait here and move ahead.

So, you have given us your opinion. Not everyone at the table is eligible to vote from the scrutiny the Agency has given to your alliances. So, I will call upon you on the left hand side of the table then.

Dr. Snider, would you like to offer your opinion?

DR. SNIDER: With the clarification that Dr. Burns gave us, my answer is "yes." I think the demonstration of efficacy as a primary series to infants would serve as a basis for efficacy of when that same vaccine is used as a booster dose in adults -- adolescents and adults.

When people say we don't have a correlate of immunity, I may be showing my ignorance, but it seems to me that there is one correlate of immunity for sure and that is having received one of these vaccines. Second, it is not clear to me that the -- and maybe people know data that I don't know -- that the absence of an immune response at

all, I haven't heard about. I haven't heard that there are people who get no antibody response.

So, to clarify that point, I think what we are saying is we don't have any -- we don't see a dose response that we would like to see and it may be, you know, because of epidemiologic factors. It may be because of qualitative differences in the antibodies, et cetera, or that we are not measuring the right things. But I think it is a little bit overextending to say that there is no correlation.

It may be that we are where we are on the curve, that we just don't see the dose response. I think that is what most people are saying when they talk about that.

DR. FERRIERI: Thank you.

Dr. Broome.

DR. BROOME: I also think, based on consistency with what we have done before and the -- I am also not aware of examples where efficacy in infants does not correspond to protection in older -- particularly adolescent and young adult populations -- I would say "yes" to the first question.

DR. FERRIERI: Thank you.

Dr. Glode.

DR. GLODE: I would say "yes" to the first

question. I am partly reassured that we can deal with this problem slightly sequentially; that is, that since an efficacy trial is planned with one vaccine, we will get answers to some of the questions that Dr. Fleming brought up. So, if it goes as predicted, it will raise antibody. It will protect and there will be a moderate prevalence of disease in the placebo group.

If all of those come out the opposite way, then I would have to re-look at this question.

DR. FERRIERI: And we will learn a lot more about adult disease that everyone is asking about.

Dr. Fleming.

DR. FLEMING: I can be brief based on my previous comments. I would be pleased to defer to my clinical colleagues here, if there judgment is that, in fact, we can translate high levels of efficacy shown in infants to reasonable evidence of some efficacy in adults. My major concern is ultimately we are looking at risk benefit and it seems to me we can't avoid the aspect that that level of efficacy matters. And I would have much more of a serious concern about saying that we can readily translate 70 to 85 percent efficacy in infants immediately to adults.

It will be important as it is in any prevention

setting, but particularly in adults where the overall prevalence of clinically relevant disease can be very much lower, that we have to understand reactogenicity very well. One approach to this whole story is the NIAID trial. There are other approaches, though, in the absence of trials.

We can use surveillance studies in follow-up to try to assess overall levels of risk and reactogenicity and efficacy and if we have a profoundly efficacious vaccine, I think we can get some real signals for that. On the other hand, if it is less than profoundly efficacious, then it is a very blunt instrument that we are using to get at a very important issue, which is what is the level of efficacy and reactogenicity in a setting where prevalence could well be a clinically relevant disease, a lot less than what it would be in children.

DR. FERRIERI: Dr. Villalta.

DR. BROOME: Could I just clarify my answer because I think the safety point is actually a very important one. I would phrase it slightly different than Tom in that I think the severity of disease that you are preventing is not that striking and our safety database available so far is not the substantial.

I don't think it is that easy to get safety

observations. So, I would encourage the manufacturers to expand their safety databases, as well as looking toward the NIAID trial.

DR. FERRIERI: Thank you, Claire. That is a really critical question that we can't overemphasize today.

Fernando, Dr. Villalta.

DR. VILLALTA: In theory, I will say "yes." Providing that the population are primed and able to respond properly -- in addition to the response, additional information should be provided about the virility of this disease in adults particularly because we don't know very well really if antibodies are effective or what class of antibodies or even if similar responses are involved.

So, I think that this information is very critical.

DR. FERRIERI: Thank you.

Mrs. Cole.

MS. COLE: I vote "yes."

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: I will be very brief. I am concerned about this question because I think it is out of the appropriate sequence. I really don't think we have a firm grip on the problem at all. And to ask this question

now, without knowing the scope of the problem -- we know that it is a relatively modest disease in terms of its severity in adults. I am very concerned about the safety issues in terms of people who are going to receive three doses of this vaccine as children and receive it again as an adult.

I think it probably is efficacious in preventing childhood pertussis in adults, but what it will do to adults with the pertussis syndrome, I am not sure.

DR. FERRIERI: Dr. Greenberg.

DR. GREENBERG: I vote "yes."

DR. FERRIERI: Dr. Clements.

DR. CLEMENTS-MANN: I vote "yes" and I agree with Claire that it would be nice to have more safety immunogenicity data.

DR. FERRIERI: I vote "yes" also, but want to support previous comments, particularly those made by Dr. Broome and Dr. Fleming.

Yes, Dr. Klein.

DR. KLEIN: Can I just clarify the NIAID's position on this trial, just for the record?

When we first initially discussed the opportunity of doing studies in adults to address all the various

issues that have been raised here, especially the outstanding public health issues -- and that was the intention of our even considering doing studies in adults was basically from a public health standpoint view -- we initially, obviously, started talking about the possibility of doing efficacy studies.

In doing so, we realized that there were a lot of -- there was a lot of information we didn't have. In fact, it was quite difficult to come up with a sample size estimate because -- or guesstimate -- because we didn't have the data. So, the 3 percent is basically just that, a guesstimate.

So, we kind of stepped back after discussing all these issues and realized that perhaps the most important aspect of doing the study was basically to answer the question about prevalence of a clinical relevant disease and we thought that was really a very primary feature to consider, maybe more important than efficacy and even as well, to look at the epidemiologic data to assess the risk factors for individuals who were immunized and non-immunized.

I think those were the two critical features of this trial that we really went to attack, rather than

purely for efficacy because we realized that there is a good chance that we might not show efficacy. But the chances of being able to demonstrate the impact on the adult population for sure is there.

I mean, I just think the way the trial is designed, we can't miss. I also feel -- we also felt that this type of data would be very relevant for the advisory groups in the future to make informed decisions and I don't think that they could possibly go ahead and do that without the data, not just efficacy data, but data on what the impact of disease is in the adult population.

One more point, in a comment about the immunology aspect, we are going to be looking at cell-mediated immunity. That is an ancillary study. We will be doing long term studies in that regard. We are also going to be looking at incidence of disease for microplasma pneumoniae and chlamydia pneumoniae because we have the patients. We have the blood and I think the opportunity is there.

So, we will have a lot more data to present than just for pertussis.

DR. FERRIERI: Thank you, David. Those are really good points.

I think we should move on to the second question.

Drusilla, why don't you reframe it for us and make sure that we completely understand it?

DR. BURNS: The question, since you have answered "yes" to the first, is demonstration of a comparable antibody response in adults/adolescents and infants an appropriate indicator that the different age groups respond to the vaccine in equivalent manners? In other words, can we use antibodies to bridge between the two age groups, as we have done between the primary series and the booster series?

DR. FERRIERI: Thank you.

Discussion from the committee?

DR. FLEMING: Not only to bridge but to conclude that the efficacy is equivalent, which is --

DR. BURNS: To conclude that there is efficacy n the vaccine.

DR. FLEMING: That is not what you say. You say in an equivalent manner.

DR. BURNS: I would like to change that and not make it such a narrow definition, but to conclude that the adults would respond the same way, such that they would be protected, so that there would be some efficacy in the adult.

DR. FLEMING: There would be more than zero -- more than zero?

DR. BURNS: It would be efficacious -- yes.

DR. FLEMING: It could be 15 percent and then the answer would be "yes." Am I interpreting you correctly?

DR. BURNS: Yes. We license vaccines on the basis of safety and some efficacy. So, that is what we want. We aren't saying that it has to be as high, necessarily. I think -- would you expect to get a reasonable amount of efficacy in the adults?

DR. FERRIERI: Okay.

Dr. Snider.

DR. SNIDER: Well, I don't think any of us know for sure, but, again, it seems to me that based on the discussions we have had, that it is reasonable to assume that one would get some degree of efficacy and based on the data we have seen in terms of titers, I would guess that it would be substantial. So, I would say "yes." Again, with my colleagues, I think there are the caveats that there are more questions to address with regard to licensure beyond these two questions, safety issue and so forth, and then for the group that I deal with, the ACIP, for those who are going to have to deal with recommendations for use of this

vaccine, there are lots of questions that colleagues around the table have raised that are going to have to be addressed before one can make those kinds of recommendations.

But in this narrow -- to this narrow question, yes.

DR. FERRIERI: Dr. Karzon, we are cutting to the chase now.

DR. KARZON: Are we voting or discussing?

DR. FERRIERI: We are doing both, Dr. Karzon. This is your chance.

DR. KARZON: I think we are on less firm ground with this second question. I postulated that the disease ought to be milder. Pertussis is a continuum of disease expression, unlike some other diseases that are more nearly all or none, although all diseases have some elements of continuum. That is why I described this more modified disease as having less bacteria for a shorter duration and less coughing as less likely to spread.

Now, one thing that is characteristic of all vaccines is that when you have a partially effective vaccine, it is most effective -- the highest efficacy rate is for severe disease and that has been true, very true in

pertussis. The efficacy with one cutoff level, say, three or more weeks of coughing, with whoops and vomiting and so on, may be 84 percent and if you look for minimal disease, it is less effective.

That also goes along with the difficulty of effacing disease so completely as to halt its pathogenesis to a lesser point. So, how this will be in real life I don't know. The critique, the down side of going ahead without an efficacy trial, there is a down side and David Klein mentioned those points to remind us, remind me of it. We will learn something with an efficacy trial that would add to our knowledge and make it simpler and easier and quicker to come to decisions about how it will be used.

I don't think there is any question of that. If we suggest that it seems to have some salutary effect without numbers, we are going to have to wait until we get epidemiological information almost. But I am suggesting that we study these patients as if they were a pathogenesis study and do cultures and so on if they get sick. Even a few cases might be instructive as to what modified pathogenesis is.

I don't know how to answer that last question.

DR. FERRIERI: That is quite legitimate. If you

feel that you are unable to answer it, I think that for this question it is a bit tougher and we can accept an equivocal.

Dr. Broome.

DR. BROOME: This is just a follow-up comment with regard to Dr. Karzon's last point.

I don't know if you were explicitly engaging this issue, but the question of when can you continue a controlled trial when there is a licensed product is something that people wrestle with. I guess I would think you can make a distinction between having a licensed product versus one for which there is a universal recommendation and in the absence of a universal recommendation, I am assuming even were this product to be licensed, that it would be ethical to continue the trial to the point when there was a recommendation for universal use or whatever.

DR. FERRIERI: Do you have an opinion on whether you can support this question then?

DR. BROOME: I wasn't -- okay, if we have moved to voting, I think this is very -- it is complex for all the reasons that have been mentioned in terms of having an appropriate surrogate, but I think, in fact, you have no

other basis. So, if you vote "yes" for the first, I think it almost implies that you vote "yes" for the second.

DR. FERRIERI: Dr. Glode.

DR. GLODE: I would vote "yes." I very much share Claire's concern that I would hope that if other products were licensed, it would not interfere with an ongoing efficacy trial and somehow that would then be stopped and we would lose all that information.

DR. FERRIERI: Dr. Fleming.

DR. FLEMING: Well, I think the question has been changed from what is written. What is written was for me fairly straightforward. So, even though you have changed it, let me give my answer to what was written and that answer is "no." We could not conclude that we would have an equivalent efficacy using the immunogenicity information.

Now, if we change the question to saying can you conclude that there is at least some level of benefit, some level of protectiveness, there may -- one may well be able to conclude that, although that is not a clinically relevant question. We are dealing with a prevention setting here and typically in vaccines, unlike a treatment setting, we expect to see evidence of more than just ruling

out no benefit. We expect to see evidence of benefit that we anticipate would translate into overall favorable risk benefit.

So, I think -- of course, you didn't change it to that. You changed it to something that -- I believe you said level of efficacy that would be acceptable; i.e., I assume meaning that would give us adequate justification to use the intervention in the context of overall reactogenicity and prevalence. And in my view, we haven't really defined that yet. We haven't defined as a committee or as a protocol team what is the level of efficacy that we would need to see in the context of anticipated reactogenicity and disease prevalence to justify a favorable risk benefit profile.

So, in a sense, I feel that I can't answer the question, although I am going to project that that level of benefit may well be in the neighborhood of what we have seen in infants, 70 to 85 percent, and conditionally given that you make that assumption, then I am led to the conclusion that, no, I can't use FHA and PT antibody level responses to infer that I will have the same level of efficacy in adults that I saw in infants.

DR. FERRIERI: Dr. Villalta.

DR. VILLALTA: Yes, I will say "yes," given into consideration the clarification made by Dr. Burns.

DR. FERRIERI: Mrs. Cole.

MS. COLE: My vote is "yes."

DR. FERRIERI: Dr. Apicella, what is your reaction to this issue now?

DR. APICELLA: I vote "no." I really don't know what the problem is basically and that is my concern.

DR. FERRIERI: That is fair enough.

Dr. Greenberg.

DR. GREENBERG: I vote "yes." I would like to reiterate that at this point I am not sure I know at all what patients I would use such a vaccine in and, in fact, I would say it is -- my indications would be extremely limited at this point. So, it is "yes," "yes," but until you better define who might benefit or what the benefits are, the utilization of such a vaccine should be extremely small.

DR. FERRIERI: Would you consider our house staff as potential candidates? You have never had an epidemic in your hospital spread by house staff?

DR. GREENBERG: I am an internist and I actually am not aware at our hospital of an epidemic among the

internal medicine house staff.

DR. FERRIERI: Spreading to all patients in the units. You are very lucky that you have not dealt with that.

Dr. Clements.

DR. CLEMENTS-MANN: I vote "yes" and I am sure we will find out who to give it to.

DR. FERRIERI: I am going to vote "yes" also, although I do have some concerns and think that we need to pursue the issues that have been presented here by some of the other members who felt more concerned about it.

There is opportunity for rebuttal for anyone who is not among the voting members to have final words on this issue.

Dr. Breiman, do you have any pearls for us or thoughts, hearing all of this?

DR. BREIMAN: Well, I am sure I have no pearls, but one thing that occurred to me that -- in response to something Dr. Karzon said before, in thinking about looking at immunologic responses in a multivariate way, I mean, I think that that is worth exploring and I wonder if people have also in developing such an approach would also be able to look at other arms of immunologic responses; in other

words, looking at CMI as well. They might come up with something very interesting.

DR. FERRIERI: Dr. Karzon.

DR. KARZON: One way to work both sides of this fence, if and when the vaccine is licensed and begins to be used in whatever recommended population, this could be studied, this introduction of the vaccine. It won't be universally used the first day and one could continue the same sort of very nice studies that are now going on in places like emergency rooms, with walk-ins, who have a persistent cough, to see those who are vaccinated by their own volition or through some device because of their age group or whatever and those who are not vaccinated and do essentially some modest pathogenesis studies on these individuals in terms of their ability to transmit bacteria.

DR. FERRIERI: Other comments from the table?

We now will move to the open public hearing and Mrs. Cherry can take over.

MS. CHERRY: I have not been notified of anyone that wishes to speak at this time. However, we will open the floor if there is someone that would like to address the committee.

There being no one, while I have the microphone,

I would say "thank you" to the committee for staying. And I will return to the chair.

DR. FERRIERI: Thank you, Nancy.

I want to thank everyone in the audience, manufacturers, for giving us such a stimulating afternoon and day. I know that we will be revisiting this whole issue, I am sure, in the future.

For those of you who are going to return tomorrow, we start at 8 o'clock sharp for the closed session.

[Whereupon, the meeting was recessed, to reconvene at 8:00 a.m., the following morning, Friday, June 6, 1997.]