available with the committee's materials, does three, dose one.

I think Doctor Hackell had a similar slide, febrile reaction rates are summarized here for the essential clinical studies. Rates of fever increased with sequential doses of whole cell pertussis, in combination with pneumococcal vaccine. When administered with DTaP and Hib rates of fever and systemic reactions did not appear to increase with sequential doses.

Fever was least frequent after dose one, regardless of concurrent pertussis vaccine. With concurrent DTaP rates of fever greater than 38 degrees ranged from five to 22 percent after dose one, 19 to 34 percent after dose two, and 19 to 28 percent after dose three.

Summarizing systemic reactions in the efficacy study, increased rates of fever were detectable above background rates, due to DTB Hib, DTaP and other concurrent vaccines. Rates of fever increased with sequential doses when pneumococcal conjugate vaccine was administered with whole cell pertussis Hib vaccine. Irritability, decreased appetite and drowsiness were also associated with pneumococcal vaccine, but without a consistent

pattern.

However, comparisons to systemic reaction rates for the meningococcal group may mask excess reaction rates attributable to the pneumococcal vaccine. When administered with acellular pertussis vaccine, fever rates and antipyretic use was greater in groups receiving 7-valent vaccine than in no injection controls. For the fourth dose of pneumococcal vaccine no safety data are available at this time to evaluate systemic reactions with the fourth consecutive dose of DTaP.

Doctor Black has provided some data on adverse events today that appear to be somewhat more updated than what we had at our disposal. This slide shows the number of deaths due to all causes through December 31, 1998. I think his slide showed 11 deaths in the pneumococcal arm and 22 in the mening. arm. with respect to overall mortality, data for all causes appear to be imbalanced with more deaths in the control arm. Causes of death in each case were provided, and none of the deaths were considered by investigators to be vaccine related.

Doctor Black also presented data on SIDS, and I think his data are actually adjusted for the first two months of life and seasonality, which is

appropriate. These SIDS data provide no reason to be concerned about use of the pneumococcal vaccine.

Again, Doctor Black presented this data earlier. All hospitalizations within 60 days of vaccine dose were entered into the safety database. The sponsor has conducted analyses of multiple safety comparisons by doses, by type of concurrent vaccine, and for various time periods after the vaccine dose. Hospitalization rates for selected diagnosis of potential interest were identified by screening against the statistical significance levels, not adjusted for multiple comparisons.

Shown here are only those diagnoses for which an imbalance in the number of cases in the pneumococcal vaccine group was apparent. Febrile seizures within 30 days and 60 days of the vaccine dose were more common in the pneumococcal vaccine group. Increased rate of hospitalization for asthma were observed. Doctor Black discussed this earlier.

The ER diagnosis of events occurring within 30 days of the vaccine dose were analyzed by concurrent vaccine. ER visits for croup within three days, breath holding within 30 days, and urinary tract infections within 30 days showed a slight imbalance of cases in the pneumococcal vaccine group. This was

presented earlier as well.

Well, adverse events occurring outside the 60 day window following vaccine doses for hospitalizations may not have been captured in the adverse event monitoring in this trial and, therefore, FDA requested that the sponsor search the hospital databases for selected adverse events related to autoimmune diseases, blood abnormalities and diabetes. These data were recently received by FDA. Events were captured using various ICD9 codes and may not be specific for a particular clinical entity as Doctor Black pointed out earlier. Preliminary review indicates no imbalance in the number of such events which would cause concern for the group receiving the pneumococcal vaccine.

Adverse events leading to study discontinuation provided an additional source of safety data. More subjects in the meningococcal vaccine control group discontinued for adverse events, 74 versus 53. The most common reasons for leaving the trial were seizures, which accounted for 83 of 127 events, or 65 percent of the subjects discontinuing. The number leaving due to seizures in both groups was similar, however. Other less common adverse events leading to study termination are shown.

Six serious adverse events were considered by study investigators to be possibly or probably related to study vaccine, three in each group. All three serious adverse events considered related to pneumococcal vaccine were seizure events.

FDA asked the sponsor to provide an integrated summary of all seizure events, in which acute events were distinguished from follow-up events, follow-up visits, or an ongoing seizure disorder by means of chart review. The sponsor has also reviewed other potential sources of information, including spontaneous reports from clinic study nurses. Using data from all sources, the number of subjects that experienced acute seizure events occurringwiththree, 14 and 30 days of study dose were assessed. Acute seizure events within 30 and 14 days of vaccine dose were well balanced across the two groups. Events occurring within three days of the vaccine dose were more common in the pneumococcal vaccine group.

Of the eight recipients of pneumococcal conjugate vaccine who had acute seizure events within three days of inoculation, seven were febrile seizures and one was afebrile, and seven had received whole cell pertussis vaccine concurrently with the study vaccines. One child had a seizure after dose one, two

had seizures after dose two, three after dose three, and two after dose four. Two subjects were also diagnosed with urinary tract infections. Doctor Black pointed that out earlier, and one subject in the pneumococcal group had a seizure after the DTaP dose, which was thought to be due to a viral infection.

In the meningococcal control group, acute seizure events within three days, two had afebrile seizures. One subject actually had a history of cerebral palsy and another had a history of seizures.

Although most seizure events did occur after concurrent whole cell pertussis vaccine, it should be remembered that most of the children in the study received whole cell vaccine with the primary series.

In supporting studies, not shown here, in supporting studies there were two additional seizure events. They occurred in the lot consistency study. One occurred four days after a dose, which was thought to be, considered to be possibly vaccine related by the investigator. The other occurred one day after the dose of the study vaccine, that was not thought to be related by the investigator, but it was certainly — related. In those two cases, the concurrent pertussis vaccine was an acellular pertussis vaccine.

Well, a safety update of hospitalization

rates and ER visits was provided for the period until December 31, 1998 as line listings, adverse events in the safety update which were considered by investigators to be possibly or probably related to study vaccines are shown. There were two seizure events reported in the pneumococcalvaccine group, one occurred eight days after a dose, and the other three days after a dose, after a fourth dose.

That concludes my discussion of the safety analysis. I'll not discuss compatibility of pneumococcal vaccine with concurrent immunizations. Responses to haemophilus influenza when administered concurrently in the primary series with pneumococcal conjugate vaccine was studied in the lot consistency study, 18-12, and in the manufacturing bridging study. Responses to Hib-PRP were significantly enhanced with concurrentpneumococcalvaccine, as shown by increases in GMCs after the third dose.

Enhancement of Hib responses when administered concurrently with pneumococcal vaccine was also observed in other and supporting studies. When administered with the fourth dose, differences in GMCs between groups were statistically significant for GMCs, however, it's been pointed out, GMC is relatively high, 22.7, and responses at clinically

significant levels were greater than 97 percent.

Responses to IPV following concurrent immunization with pneumococcal vaccine and IPV in the primary series was evaluated in a single study. That was the manufacturing bridging study. IPV was administered at two and four months of age. Serum neutralizing titers were determined at seven months. Data for the preferred manufacturing lot only is shown here. Highlighted are responses to serotype one, for which the lower 90 percent confidence interval for the difference in percent zero responders at an antibody titer of one to ten was 13.3 percent, thus a ten percent difference could not be ruled out.

No interference was seen with polio type two and type three. The clinical significance of this apparent interference with IPV one responses is not clear. No other studies in the application address concurrent immunizations with IPV.

Compatibility with acellular pertussis responses in the primary series was evaluated in study 18-12. The control group received concurrent vaccines only, and the table show data for the three private lots of pneumococcal vaccine were pooled for comparisons to control. A four-fold rise in responses to Fimbriae was 45 percent versus 62.5 percent in the

control group. The 90 percent lower bound of the difference exceeded 30 percent. Responses to pertactin were also lower in the concurrent pneumococcal vaccine group. Pertussis toxoid and FHA antigens did not show decreased responses with concurrent pneumococcal vaccine, and no data are presented in the PLA addressing responses to pertussis antigens after four consecutive doses of DTaP.

Concurrent use of pneumococcal vaccine and MMR were studied in a very small group of infants in an early supporting study, although no direct comparisons were made the percent seroconverters to mumps and rubella are low by historical standards. The FDA does not view these data from this small study as definitive.

I'll now talk a little bit about catch-up schedules. The sponsor has proposed a catch-up schedule for previously unvaccinated children, which is reproduced here from the vaccine label, from the proposed vaccine label. The catch-up schedule is based on comparisons of immunogenicity data, using these regimens to antibody levels achieved after three doses by children in the efficacy study.

For the catch-up schedules proposed, available data are summarized in this table. Safety

data are limited to 24 subjects who received three doses between seven and 11 months of age. There's no safety data for subjects, excuse me, for the age interval between 12 and 24 months of age, and for children greater than 24 months of age there's only data available for use of the 9-valent formulation which was collected among Israeli infants.

An additional study intended to support catch-up schedules was recently received by FDA. Data files supporting the study results have not yet been submitted to FDA for review. Therefore, the committee will not be asked to comment specifically on the adequacy of the data to support the proposed catch-up schedule, however, general comments on catch-up are welcome.

This slide is intended to show that when pneumococcalvaccine is given concurrently with either whole cell or acellular pertussis vaccine GMC titers after the third dose are comparable.

The efficacy trial provided data to assess protection after three doses until the fourth dose was administered, and subsequently after the fourth dose, to make inferences about long-term — longer-term protection it may be important to assess antibody levels after dose four.

In this table, GMC is attained using the various catch-up schedules, are compared to GMC schedule, GMCS attained in the efficacy study after doses three and four, so the efficacy study results are on the right and the proposed catch-up schedule data that is available from the proposed catch-up schedules is on the left, and it's broken down by serotype.

Post-dose four GMCs exceeded two micrograms per ML for all serotypes. Response to the fourth dose was least robust for serotype 19f. Serotype 19f, which is the serotype of the only case of invasive disease among the fully vaccinated infants — for serotype 19f, which is the serotype that the only case of invasive disease among fully vaccinated infants in the pneumococcal vaccine group, GMCs obtained for the three dose catch-up schedule between seven and 11 months of age, which is 1.6 micrograms per ML, exceeds the levels achieved post-dose three, but does not achieve levels post-dose four.

That's all I have to say about the catch-up schedules, and finally, an essential component of the license application is to demonstrate ability to scale up production from private lots used in the clinical studies to manufacturing scale lots. Vaccine produced

in manufacturing scale as compared to private lots, in terms of safety and immunogenicity, the sponsor prepared two full-scale lots for comparison in the manufacturing bridging study, the design is shown here, about 175 subjects were enrolled for each, for the pilot scale lot and for the two manufacturing lots. Acceptable criteria for demonstration of bridging were less than a two-fold difference in GMCs, and less than a ten percent difference in sero responders.

Well, the most appropriate antibody level on which to base sero responsiveness engendered much discussion. The antibody level associated with protection for invasive disease is unknown. Moreover, it's not clear that a single level is appropriate for each of the seven serotypes.

The antibody levels chosen to define sero responsiveness are illustrated in this slide. The antibody levels chosen were based on the maximal difference between immunized and unimmunized infants at seven months of age, and so the black curve, or the one that looks like a parabola, that is the difference curve, and the top of the difference curve then served to define the sero responder level.

Thresholdvalues were determined for each of

the seven serotypes which are shown here. This is a busy slide, but it does show that acceptance criteria for sero responsiveness were met for each of the seven serotypes. You can look at the far column on the right, that is, 90 percent lower limit of the difference between sero response rates for the pilot and the manufacturing lots did not exceed ten percent.

GMCs was the co-primary endpoint in the bridging study. GMC criteria were also met for all seven serotypes, that is, the 90 percent lower limit of the ratio of GMCs fell between .5 and two, thus, FDA accepts that clinical evidence of bridging has been demonstrated.

The last couple of slides have to do with the lot consistency study. This is the study designed for the lot consistency study. The three lots, three private lots of vaccine were compared, 75 subjects were enrolled for the group, and infants received concurrent immunizations. The criteria, acceptance criteria were that GMCs would not differ by more than two-fold. The multiple comparisons were, by nature, seven serotypes and comparisons between three lots, there were multiple comparisons, actually three comparisons marginally exceeded the criteria. However, because they only marginally exceeded, and

because of the multiple comparisons FDA does accept the clinical evidence of lot consistency as demonstrated.

Well, that concludes the presentation. I'll now present the questions to the committee, and then this afternoon we'll represent the questions.

Do the data provide sufficient evidence of efficacy against invasive disease for Prevenar as it was studied in the efficacy trial, that is, after administration at two, four, six and 12 to 15 months of age? If not, what additional information should be requested?

The second question, do the data provide sufficient evidence of safety for Prevenar? If not, what additional information should be requested?

The next two are not questions, but number three reads, please discuss the data regarding concurrent use of Prevenar with other vaccines administered according to the recommended schedule of infant and childhood immunizations.

And, lastly, please provide — please identify any issues that should be addressed by post-marketing studies.

CHAIR GREENBERG: Thank you, Doctor Pratt.

We now have a little more time for the

panel, for the committee to ask some questions, and I would remind you that you can address Doctor Pratt, or if you have some lingering questions from the manufacturer, for the manufacturer, perhaps, you could bring them up now.

I know Doctor O'Brien had a question.

DOCTOR O'BRIEN: I did, but I think Doctor Pratt answered it, but I'm going to make sure he did, so this is actually addressed to Doctor Pratt.

I was concerned by the fact that there were eight percent African Americans represented in the Kaiser study, and whether or not they'd be able to show in the efficacy data that in that group which appears to have an increased susceptibility to pneumococcal invasive disease, that they could show some efficacy in that group. But, because Doctor Pratt said that there was a higher representation of African Americans in the invasive disease group, which pretty much was the control arm of the study, I feel more comfortable that they were able to show that even in this more susceptible group there appeared to be efficacy. That's my summation from what Doctor Pratt said.

CHAIR GREENBERG: Does anybody want to comment on that summation, or was it just simply-you

can simply say it's correct if you want.

No comments? Okay.

Doctor Snider?

DOCTOR SNIDER: Doctor Black made comments about multiple comparisons, when he was talking about health outcomes. Doctor Pratt just talked about multiple comparisons and he talked about lot consistencies, but nobody talked about multiple comparisons when they were talking about the interference or potential interference between vaccines, but I wondered if someone had looked at that and whether there are patterns there that should be of concern to the committee.

It's hard for me to dig out from what was presented to us whether there is a pattern of the 7-valent pneumococcal conjugate vaccine seeming to diminish responses to certain things, increase responses to others, or whether there is a pattern toward diminished responses, which I think would be quite different.

So, if someone could clarify those comparisons for me a little bit better, I would appreciate it.

CHAIR GREENBERG: In order to — I'll ask first Doctor Pratt if he wants to, for the FDA, to

clarify, and then ask the manufacturers whether they have anything additional to add.

DOCTOR PRATT: Yes, I think multiple comparisons are an issue. I think that —

DOCTOR GOLDENTHAL: Well, I think that there were some differences that, perhaps, the committee should look at and focus on. I think for the IPV it was polio type one, and for pertussis there was some differences known for pertactin and fimbriae.

These, you know, in talking-but there were no differences noted for pertussis toxin — in talking with regard to pertussis, in talking with staff of the pertussis labs who deal with this on a very regular basis, they thought it was difficult to make an exact clinical determination — you know, a clinical correlation, if you will, to these differences.

With regard to IPV, it was pretty close. It was, I think, 89 percent with simultaneously administered 7-valent pneumococcal vaccine. So, these may be, you know, again, they are multiple comparisons with the — even within looking at pertussis there were multiple comparisons, so I think that's something that can be considered.

This also might -you know, these also might be things that are addressed with post-marketing

studies.

CHAIR GREENBERG: I'm going to just push you a little bit, Doctor Goldenthal. That was a perfect — that was a politically correct answer, but I'm not sure that was all — it wasn't, for somebody like me, a dummy, that wasn't that helpful an answer. So, the critical question here, is it clinically relevant, do you think that this vaccine is going to affect other vaccines, and let's just take polio, that was the simplest one. Is there the feeling, when you talk to your colleagues about the effect of the 7-valent pneumococcal vaccine, that there's a worry that it affects immunity to polio type one after delivery?

DOCTOR GOLDENTHAL: I believe that we would accept those data. However, we still may ask for an additional follow-up study.

CHAIR GREENBERG: I think the key here is with all vaccines we want additional follow-up study, but the most important thing for the committee to know is whether you think that — what's your likelihood that there's going to be a real biologic effect. So, you are saying you think there probably would — your bet is no.

First, Doctor Myers, then Ms. Fisher.

DOCTOR GOLDENTHAL: By the way, let me just

add one thing about polio, that antibody was assessed seven — at the seven month time point, and the doses of polio vaccine were given at two and four months.

DOCTOR MYERS: A related question, I was wondering, has concomitant use of other HIV conjugate vaccines been examined for interference? The HIV conjugate data presented was with the same CRM_{197} carrier protein, but what about outer membranes, protein conjugates and so on?

CHAIR GREENBERG: Can either the FDA or the manufacturer answer that question?

Doctor Siber?

DOCTOR SIBER: Let me comment on the first question from Doctor Snider, and then address Doctor Myers' question.

I think you can divide the apparent differences and responses with and without pneumococcal vaccines into two types. The ones that have already been addressed of unrelated antigens, where I think mechanisms are pretty unclear, where many, many comparisons were done where some differences were found.

And then the second group is ones which are with antigens that are related in the sense that they have the same carrier, and so we did see significant

and convincing evidence of interactions between the Hib vaccine using the same carrier as the pneumococcal vaccine.

We were fortunate that in the primary series, when we were most concerned about producing antibody levels quickly, that was a positive interaction, and the way at least one immunologic theory for that is that it limits how quickly you make antibody to the polysaccharides is how much T-cell help you have induced to the carrier molecule CRM, and during the primary series that seems to be better when you have more CRM in the form of conjugate.

We also showed that there was a significant reduction at the time of boosting in the response to Hib, and that's a kind of interference, and although significant, because the levels were very high it didn't seem to be of clinical importance.

The question Doctor Myers asked is, what would one see with an unrelated carrier, such as a tetanus-based pneumococcal conjugate or a tetanus-based Hib conjugate would be more relevant, we don't have data addressing that, but the theory I've just mentioned would suggest there wouldn't be a problem by adding a CRM-based pneumo conjugate to a regimen where Hib T was being used, or Hib 0 and P was being used,

but we don't data directly addressing the question.

CHAIR GREENBERG: Thank you, Doctor Siber.

Ms. Fisher?

MS. FISHER: Yes, I have two questions, one to Doctor Platt and the other to the vaccine manufacturer. But, Doctor Platt, I want to congratulate you on this analysis that you provided to the committee, I thought it was excellent.

I guess I'm confused. We are being asked to look at invasive disease efficacy. What is the efficacy rate with this vaccine with all the data that you have, with regard to invasive disease?

DOCTOR PRATT: At the primary analysis, it was 100 percent. At the follow-up analysis, my understanding is it's 97 percent, or in that range.

MS. FISHER: With invasive disease, okay.

The manufacturer, local reactions, fever, irritability, drowsiness, decreased appetite, seizures, are more frequent in the pneumococcal vaccine group when compared to controls. Has the manufacturer tried to determine the biological mechanism for these increased local systemic and neurologic reactions, and whether there are genetic or other differences in the children who are suffering these reactions versus those that are not?

DOCTOR SIBER: I think we need to discriminate between the reactogenicity of the vaccines, such as tenderness, and pain, and redness, and swelling, fever, which I think is seen with all vaccines essentially, to a greater or lesser extent, which are mild transient, self-limited. Those were, I think, with this vaccine in a similar range that we have seen with childhood vaccines generally, and we were not alarmed by them, and I must say the mechanism presumably is that there are lymphokines released and cytokines released in the course of a normal immune response, and it's part and parcel of inducing immunity in people, you can't avoid that.

With regard to rare severe events, I think you saw quite an extensive and elegant database that our colleagues at Kaiser have assembled of baseline rates of rare severe events, chronic events, compared to the two groups that we have studied, and a very large number of children, and all we can do to further hone that down is to also look at intervals close to vaccine administration for any suggestion of a temporal relationship.

And, our interpretation of those data were that we really couldn't see anything that suggested a relationship to a severe event.

CHAIR GREENBERG: Any — Doctor Stephens?

DOCTOR STEPHENS: I have a couple of questions regarding the surveillance part of the Kaiser study, and that had to do with whether there were — was antigen positivity looked for in culture negative cases in meningitis, for example, and was that a part of the study?

DOCTOR BLACK: We did not look for that, because the primary outcome here was serotype specific efficacy, and there really is not a technology that I'm aware of to look at that.

And, antigen tests are done at the physician's discretion, but we did not do them, institute them, as part of the study design.

DOCTOR STEPHENS: The second question as a part of the surveillance has to do with how many children were, in fact, lost from your surveillance pool, and, obviously, there were a number of children who received one dose and then were subsequently lost. Do you have that exact — that number?

DOCTOR BLACK: Overall, about 15 percent of the total follow-up time was lost due to drop out over the study period of about four years. Does that answer your question?

DOCTOR STEPHENS: And, that drop out was both

children who may have moved or left the area, and children who decided not to complete the course of the study.

DOCTOR BLACK: Well, children who did not complete the course, the children who were still members of the health plan were contacted by the study nurses routinely to try and get them in, but, obviously, we could not coerce parents to come in, it's a voluntary participation.

The total number that actually went on to get dose four, for example, by the end of the 15th month, was — most of the children in the study did continue participation throughout. In terms of cases, I guess what you are asking, could a case occur outside that we would not be aware of. You know, there were cases of disease and adverse events were identified outside the system, we tried to the best of our ability to identify all cases. We are not aware of any cases that occurred outside the system, either in people who were members of the health plan or people who had left. And, people within the area where we were at were aware of the study, had been contacted, and had been asked to report any events back to us.

DOCTOR STEPHENS: Did you say there were two

additional cases since the April analysis was submitted?

DOCTOR BLACK: There have been two additional cases.

DOCTOR STEPHENS: In vaccinated individuals?

DOCTOR BLACK: In vaccinated individuals. They are both in the control group.

CHAIR GREENBERG: Doctor Estes, and then Doctor Globe.

DOCTOR ESTES: In the -when you had children dropping out and not finishing the fourth dose, did your study nurses ask the parents why they didn't want to continue, or was that not possible?

DOCTOR BLACK: The most common -you know, we had children, there were about three percent of children who were still members who did not go on to get their — did not go on to get their fourth dose within that time period. A substantial percentage of those did receive the dose, but after that time window. It has to do with this many people, 97 percent we actually thought was pretty good.

CHAIR GREENBERG: Doctor Globe.

DOCTOR GLODE: I had sort of a two-part antipyretic question for Doctor Black. Don't leave.

If I recall, someone this morning, and I

don't recall if it was you, that were talking about excess visits for ingestion/poisoning, and I'm wondering, were any of those, you know, accidental Tylenol overdoses from treating fevers, or febrile seizures, or whatever? That's part one.

DOCTOR BLACK: Okay. We looked at those over in terms of time period in a similar graph to what I showed you this morning, and they are spread out also over the surveillance period. We've not looked to see which ones are due to Tylenol and which ones are not. We'd have to go back and do that, but there was no clustering of those events close to receipt of vaccination.

DOCTOR GLODE: I see, and the second part of that was, in the actual design of the study, were the patients that were enrolled specifically not given any antipyretics at the time of administration of the vaccine, but then what type of instructions were given to people about using antipyretics?

DOCTOR BLACK: Yes, the use of antipyretics was at the discretion of the physician, and actually it's one of the questions we asked during the telephone interview, and I can tell you that with children who received the whole cell vaccine that antipyretics were used routinely in about 90 percent

of those children, and that number is about 80 percent in the DTaP recipients.

DOCTOR GLODE: But, used not at the time the vaccines were administered in the physicians' office, but used later by the family?

DOCTOR BLACK: No.

DOCTOR GLODE: Oh, used at the time.

DOCTOR BLACK: Used at the time. That's distinct at our site from the Colorado data where it was not used routinely.

CHAIR GREENBERG: I'm going to let this go a little further, because this is important.

Doctor Ferrieri and then Pamela Getson, who is in the audience, who is an FDA statistician over there, and then Doctor Daum.

DOCTOR FERRIERI: I had a different type of question for the sponsors. Do we have an understanding of the genes that regulate the synthesis assembly of pneumococcal polysaccharides as we have some notion of in Group B Strep., and if you know this then do you see some future for application of PCR to address the question about looking for other serotypes that were not vaccine, or that might have been the vaccine serotypes on body fluids such as CSF. Where are we in our state of knowledge on applying that type

of basic science to the diagnostics?

DOCTOR SIBER: There is quite a bit of understanding, which I'm not an expert in, there's an advocate locus where capsules are made. They are typically clustered genes, and it's a particular locus in the pneumococcus, which is one of the reasons that the capsule machinery can be exchanged by transfection.

My understanding of the PCR assays that have been developed to date for the pneumococcuses, they have not focused on the capsule machinery for the probes, but for some common DNA sequences, common to all pneumococci.

Theoretically, it may be possible to get type-specific probes, but to my knowledge, unless somebody else in the audience can comment, that hasn't been done yet.

DOCTOR STEPHENS: Such assays are being developed for meningococci, for example, and are working actually quite well. I don't see why they couldn't be developed for pneumococcus.

DOCTOR FERRIERI: I know that.

CHAIR GREENBERG: Doctor Getson?

DOCTOR GETSON: I'd like to make sure that we are all clear about both what we in CBER FDA

presented, as well as our response and the committee member's question regarding race and ethnicity. We are going to try to put up our slide, and Doctor Pratt can speak to it if necessary, but I want to be clear about something that I think I heard different in terms of the question from the committee member, Doctor O'Brien.

Here on the top two lines you see the relative representations of the different ethnic groupings that were in the efficacy study. Below the middle line you begin to see the relative proportions represented among case invasive disease, and you see the 17, the 40 and the 61 represent the various time points for which these analyses were produced.

Now, when I use the word over representation, I think sample, and I believe our committee member had a question that would most closely parallel over representation in a sample. That is not what this slide can give you information on, and, perhaps, you want to revisit, in fact, the question you were asking. The over representation would be among the invasive disease cases, and clinically Doctor Pratt can comment more, or, perhaps, you want to go back to the committee with questions.

DOCTOR O'BRIEN: That's exactly what I meant,

though. If they are over represented in the invasive diseases, and since the vaccinated group overall with the pneumococcalvaccine were not getting the invasive disease, I felt better that we would be able to see a difference in that small subset of more susceptible individuals.

DOCTOR GETSON: Good. Several of us weren't sure whether you had intuitive that there was an over representation per the sampling. So, we wanted to get that slide up so it was clarified.

DOCTOR O'BRIEN: No.

DOCTOR GETSON: Good.

CHAIR GREENBERG: And, I think Doctor O'Brien had it right, and —

Doctor Daum?

DOCTOR DAUM: I have a comment and then a question for FDA colleagues. The comment is that in addition to capsular typing there are a number of DNA based technologies in place and being developed for differentiating, or fingerprinting, if you will, different pneumococcal isolates. And, I think that in terms of following serotypes and changes in epidemiology following introduction of immunization, these will be helpful and I have no doubt that more people will get involved with looking for genes that

are sufficiently genetically diverse that allow fingerprinting by molecular-based techniques.

The question that I have is, we've heard some data from Doctor Pratt about inferences regarding the protective concentration of antibody based on the trial that we saw this morning, and I guess I'm anticipating that things are going to go smoothly in terms of approval of this vaccine, and I'm looking down the road to think that there will be other vaccines introduced for consideration, and wondering whether the FDA has given any thought yet to bridging, or how to bridge between what we saw this morning and different candidate vaccines, and whether the numbers that Doctor Pratt showed us, as best guess estimates of protective antibody concentrations, will, in fact, be those bridges.

CHAIR GREENBERG: I'm just going to — that is a question that even somebody out of the field like myself realizes could take two to six days to answer. So, give us, you know, a global point of view, since we don't have to have a definitive answer at this point.

DOCTOR GOLDENTHAL: That will be the subject of a future Advisory Committee meeting, but actually I can make a couple of quick comments. You know, it's

a difficult area. I mean, because the vaccine was so highly effective there were — and relatively few failures, and in addition to that there wasn't correlation between post-vaccine immune response in even those few failures in the study that really I don't believe that it's possible to say exactly, you know, what level is protective.

In the event that an immune — that some type of an immune response would be acceptable, I think the most logical approach would probably be one of looking at the immune response of a different vaccine, if you will, with using a non-inferiority approach, with a pretty tight confidence limit.

CHAIR GREENBERG: I am going to call a halt now. It is now, by my watch, 12:20, and I'm going to resume right on time with the schedule, so we have 20 minutes for — we can have one question now from our statistician, and then you are all back at 12:40 to continue.

DOCTOR HARTIGAN: I have a question for the FDA. How concerned is the FDA in considering safety that the control group in the major study was not an active control, and was not an approved product?

DOCTOR GOLDENTHAL: Well, we would agree that that does pose certain limitations, and the data have

to be viewed in that context, including the reactogenicity data. I mean, you know, I think Doug covered it quite well in his presentation. I think that there is, you know, additional local and systemic reactogenicity added by having the 7-valent pneumococcal vaccine.

In terms of comparing some of the unusual events, I think that the comparison to the pneumococcal — to the meningococcal vaccine can still lend itself to some valid analyses. Obviously, we are also interested in some of the historical background rates of some of these events, but I would agree that having the meningococcal vaccine as the control does add a complexity to the interpretation of the data.

CHAIR GREENBERG: Okay. I'm going to close it down. I'll see you all in about 12 minutes, about 17 minutes.

(Whereupon, the meeting was recessed at 12:23 p.m., to reconvene at 12:43 p.m., this same day.)

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

(12:43 p.m.)

CHAIR GREENBERG: If people could take their seats, please. I think we need to hand out complimentary Turns along with —

Does the manufacturer make an H2 blocker or a proton pump inhibitor?

So, again, I'd like to thank all of you for being so expeditious, and I'm sorry to push you so hard, but I really want as many panel members as possible here to go over the questions.

So now, we are going to have, and again, please, everybody stick to your time limits or be quicker, so now we are going to have Doctor Kilpi from Finland give us a brief talk about otitis.

DOCTOR KILPI: Thank you, and good afternoon, everybody. It's an interesting experience for me to be here.

I'm going to tell you about results of the Finnish otitis media vaccine trial, which evaluated the efficacy of — conjugate vaccine against acute otitis media.

This was a large trial and, therefore, we had a very big study group, too, and these are the names of persons responsible for certain key areas in

the trial.

The clinical phase of the study was started in December, '95, and ended in March, '99. The study was conducted in Finald in Tampere, which is in the Finnish scale a middle-sized city with a population of 200,000, and in two smaller municipalities, Nokia and Kangasala, which are located close to Tampere.

During this time, we enrolled 1,662 children in the trial, and they were all randomized to receive either Pnc CRM or the control vaccine which was hepatitis B vaccine in our trial.

The children were followed from two to 24 months of age at study clinics which were especially established for the follow-up. The follow-up consisted of scheduled visits and sick visits, and the aim was to evaluate and treat all respiratory infections requiring medical attention at the study clinics.

And, these were the vaccines used in the study, so all these children received either Pnc CRM vaccine or recombinant hepatitis B vaccine in a randomized fashion, blinded fashion, at two, four, six and 12 months of age. In addition, they received whole cell DTB Hib combination, IPV and MMR.

This was the definition for acute otitis

media we used. First of all, we required that there has to be symptoms of acute infection, which could be almost anything, fever, earache, irritability, diarrhea, vomiting, otorrhea or any symptoms of respiratory infection, and then there had to be some signs of acute otitis media that is a visually abnormal tympanic membrane suggesting middle ear effusion.

In this trial, we really wanted to know what is the microbial course behind the case, what causes the acute otitis media, and that's why whenever acute otitis media was diagnosed myringolomy was performed and a middle ear fluid sample aspirated for bacterial culture and chemical serotyping when needed.

We also need a definition for acute otitis media episodes for our analysis because as you very well may know acute otitis media is something that tends to repeat in the same individuals over and over again. And, we defined that acute otitis media episode starts at diagnosis and lasts for 30 days, so after 30 days a new episode could start.

We also focused on safety. The parents were asked to record local and systemic reactions on diary cards on the first, second and third day after each vaccination. Information on all serious adverse

events was collected and reported, and also in this category the unexpected adverse events considered possibly, probably or definitely related to the study vaccine were reported.

Randomization went very well. We have 831 children in the Pnc CRM group and the same number of children in the control group. Our discontinuation rate was very low, 82 subjects had to be excluded from the per protocol analysis at some point, and only 65 dropped out from the follow-up, so that's four percent of all.

Here are some baseline characteristics of the study population, just to show that there is no over representation of either sex, prematurity, low birth rate in either of the treatment groups. Maternal education score was also very similar in the treatment groups, and so was the number of children living in the same household.

Daycare attendance is a known risk factor for acute otitis media, and in our study the proportions of children attending either daycare center or family daycare were similar in both treatment groups throughout the follow-up.

Breast feeding was also equally common in both treatment groups, 54 percent of the children were

breast fed for longer than six months, and very few families admitted smoking.

Okay, then to the results. This is the only slide I'm going to show about local reactions, but it very well represents the whole picture. This is tenderness. Local reactions after Pnc CRM vaccines were more common than after hepatitis B vaccine, but on the other hand they were less common than after either the Hib combination that was given concomitantly with the first, second and third dose of the study vaccine.

Fever was more common in the Pnc CRM group after vaccination than in the control group, and this may be a little bit confusing to look at the rate of proportion of those with fever increases dose by dose and then suddenly drops, but I can remind you of the concomitant vaccine which was here, DTB Hib, whole cell DTB Hib combination and here IPB, so that explains it.

There were 160 SAEs, serious adverse events, or related unexpected adverse events in the Pnc CRM group, and 194 in the control group. None of them was assessed by the investigators to be probably or definitely related to the study vaccines, and ten were considered to be possibly related to the study

vaccines.

And, this is what they were, there were altogether six events in the Pnc CRM group, four of them were skin reactions. They were not serious adverse events, did not result in hospitalization, but were considered unexpected by the investigators and were, therefore, reported in this category. There was one event with a case of independent neurologic symptoms, which was a child hospitalized because of excessive crying, had at the same time fever and the child had just received DTB Hib combination and Pnc CRM vaccine, had also local reaction on the DTB Hib site.

This one other reason was a transient neutropenia case.

Here are some of the more severe serious adverse events which were not considered to be in any way related to the study vaccines. There was one death in the Pnc CRM group which was caused by intestinalobstructiondue to congenital malformation. There was one hypotonic hyporesponsive episode in the control group and one invasive bacterial infection in the Pnc CRM group. This was caused by — a non-vaccine serotype for invasive bacterial infections in the control group. Two of these were pneumococcal

infections caused by vaccine serotypes, one pneumococcal disease caused by a non-vaccine serotype and one meningococcal meningitis.

Okay. Now, I'll move onto efficacy. First of all, we looked at AOM, acute otitis media, regardless of etiology, how many episodes there were overall. In the Pnc CRM group there were 1,251 acute otitis media episodes, and in the control group 1,345 episodes, which means that the vaccine reduced the number of any AOM episodes by six percent, and the difference between Pnc CRM and control group is not here statistically significant.

Okay. Then we looked at culture pneumococcal acute otitis media, irrespective of serotypes, and there were 271 episodes caused by pneumococcus in the Pnc CRM groups and 414 in the control group. The vaccine efficacy against pneumococcal acute otitis media was 34 percent and this time the diff'erence is statistically significant, 95 percent confidence intervals are from 21 to 45 percent.

This was our primary endpoint, acute otitis media due to vaccine serotypes, and this is our primary analysis which is the per protocol analysis. The per protocol follow-up period started 14 days

after the third dose. And, during this follow-up period we had 107 AOM episodes due to vaccine serotypes in the Pnc CRM group and 250 in the control group, and, thus, the vaccine efficacy against acute otitis media due to vaccine serotypes is 57 percent, 95 percent confidence intervals are from 44 to 67 percent.

These are the results for the same endpoint analyzed by intention to treat, and the intention to treat follow-up period started on the day of the first vaccination, and here the efficacy looks very similar, it's 54 percent.

We also looked at vaccine efficacy by dose, so from dose one to dose three, et cetera, and there seemed to be some efficacy already after the first dose, it increased after second dose, and reached kind of steady state after the third dose. So, the endpoint is acute otitis media due to vaccine serotypes.

And, this is the summary of the efficacy results, vaccine efficacy against acute otitis media due to vaccine serotypes, 57 percent, pneumococcal acute otitis media overall 34 percent, and any acute otitis media six percent.

And, the FinOM study group concludes that

heptavalent pneumococcal conjugate vaccine Pnc CRM is safe, it causes more local reactions than hepatitis B vaccine, but significantly less than DTB Hib combination.

There were fewer serious adverse events in the PRC CRM group than in the hepatitis B vaccine group, and there was no apparent association of any severe events with Pnc CRM vaccine.

We also conclude that the vaccine is efficacious against culture confirmed serotype specific acute otitis media and culture confirmed pneumococcal acute otitis media.

Thank you.

CHAIR GREENBERG: Thank you, Doctor Kilpi.

We have time for a few questions, if there are any.

I'm sorry, Doctor Kim?

DOCTOR KIM: Can you somehow elaborate the phases of protection against acute otitis media following vaccines? So, what is the sort of postulated mechanisms of protection against acute otitis media?

DOCTOR KILPI: You mean how the infection that is actually here kind of superficial can be prevented by a vaccine. Well, the assumption is that

the antibodies affect also the mucosal surfaces, but we don't know about that yet. We have collected saliva samples to assess that.

CHAIR GREENBERG: Doctor Daum?

DOCTOR DAUM: I have two questions for you. The slide went up and down quickly, and I may not have read it right, and apologize if I'm wrong, but I thought I saw some efficacy estimates after various numbers of doses, and I thought that the first two doses had very wide confidence intervals, which had wide overlap with zero. And then, I thought you said that the vaccine already had efficacy after one or two doses. Did I misunderstand?

DOCTOR KILPI: I said the vaccine seemed to have efficacy.

DOCTOR DAUM: Not to mince words here, but do you want to revise that statement? I can go on to my second question, I guess.

CHAIR GREENBERG: Why don't you go on to your second question.

DOCTOR KILPI: Yes, it's not statistically significant after dose one and dose two, between the interval, no, but the trend I think is very beautiful.

DOCTOR DAUM: The second question is, as I recall this trial initially had more than one

pneumococcal vaccine in it. Can you clarify that for us and tell us what happened to the others?

DOCTOR KILPI: The vaccine had — the trial had three arms throughout, and there were two conjugate vaccines involved, and the evaluation of the third arm, which was another pneumococcal conjugate vaccine, that has not yet been done.

CHAIR GREENBERG: Doctor Stephens?

DOCTOR STEPHENS: Was ear tube placement looked at as an endpoint in this study?

DOCTOR KILPI: It was not an endpoint in the analysis plan or in the protocol, and we are going to do the analysis, but it has not been yet done yet.

CHAIR GREENBERG: Okay,

If there are no other questions, I think we can move on and, Doctor Pratt? Okay, excuse me, I'm sorry, I'm moving too quickly.

Questions, comments, summary and presentation of questions.

Yes, Doctor Pratt, you are up, Doctor Pratt.

Ah, Doctor Black?

DOCTOR BLACK: Thank you, Harry.

I just wanted to make one quick comment in response to Doctor O'Brien's question, in terms of race specific efficacy. We did, during the brief

lunch, look at the case split in African Americans, and the per protocol analysis the case split is 11 and the control group zero in the pneumococcal group, and in the intent to treat analysis that's 13 in the control group and one child who was partially vaccinated with one dose in the pneumococcal group.

DOCTOR O'BRIEN: Thank you.

CHAIR GREENBERG: What I'd like you to do, Doctor Pratt, is just go over these questions again, and then we're going to have an opening to public hearing, where people in the audience who wish to make a statement can, and then we will return to these.

DOCTOR PRATT: Okay, sure.

Questions for the committee are these, do the data provide sufficient evidence of efficacy against invasive disease for Prevenar, as it was studied in the efficacy trial that is, after administration at two, four, six and 12 to 15 months of age? If not, what additional information should be requested?

Number two, do the data provide sufficient evidence of safety for Prevenar? If not, what additional information should be requested?

Three, please discuss the data regarding con current use of Prevenar with other vaccines

administered according to the recommended schedule of infant and childhood immunizations.

And, number four, please identify any issues that should be addressed by post-marketing studies.

CHAIR GREENBERG: Thank you, Doctor Pratt, and, committee members, as you listen to the open public comments I'd like you to cogitate on these questions and formulate your thoughts in a very clear way.

Do we have anybody in the audience who wishes to make a public statement? Could you please identify yourself?

DOCTOR CLASSEN: My name is Bart Classen, I'm a vaccine researcher, and today I'm going to talk to you about our data that was published two weeks ago in the British Medical Journal, suggesting that the haemophilus vaccine – haemophilus influenzae B vaccine is likely to cause insulin-dependent diabetes. The reason this is pertinent to today's discussion is that we've heard from several people that the haemophilus influenzae B vaccine is very similar to what is in the pneumococcalvaccine, in that they are both conjugated polysaccharide vaccines. The difference is the haemophilus influenzae B vaccine is a single vaccine, it's against a single capsular strain of organisms,

whereas the pneumococcalvaccine that we're discussing today is really seven different vaccines, it's against seven separate strains, capsular strains of pneumococci.

We are going to talk about insulin-dependent diabetes, which is an autoimmune disease. It's a marker for other autoimmune diseases, but it is relatively easy to study compared to other autoimmune diseases. The theory, or this data is that as you stimulate the immune system you are going to increase the risk of autoimmunity. We were able to follow up on a large prospective clinical trial in the haemophilus influenzae B vaccine in Finland, essentially, all children in Finland over a two-year period were put into this study, it's 114,000 children, which would range by having either received four or one dose of the haemophilus vaccine. And, because of the design of the study the control group were the children that were born in the two years prior to the study.

And, this is some of the data. It's important to note that the data that Doctor Black said that were only about two years follow-up, and the curve was essentially identical at two years, they separate starting around three and a half years, and

you get really nice separation around seven years.

And, this is the data with ten-year follow-up. There are an extra 58 cases of diabetes in the group that got four doses versus the group that got no doses, and then there are about 36 extra cases per 100,000 in the group that got one dose.

What we want to do is get some additional data support causality, and so we did some subgroup analysis looking at the five to nine year old children. And, as you can see here, there is an increase in diabetes, about an extra 32 cases per 100,000 in the groups that were five to nine, versus the group that didn't get vaccine.

And, here's the temporal data. This is the instance of diabetes in Finland year to year from 1967 through 1995, and what you see is in the five to nine year old period it had been stable for about ten years or more, until the group that got the vaccine entered this age group and then the instance of diabetes shot up quite dramatically. The incidence also had shot up after the measles, mumps, rubella vaccine had been added, and after a more potent pertussis vaccine had been added as well.

But, the take-home message with the haemophilus vaccine is that we had a very straight

incidence of diabetes until the haemophilus influenzae B vaccine group reached this age group. This is strong support for causal relationship.

Other data that support a causal relationship is that in other areas of the world, where the haemophilus vaccine was added, we'd expect that we'd see a rise in diabetes, in fact, that's what we saw. Several centers now in the U.K. have reported rises in diabetes following the haemophilus influenzae B vaccine. This is Oxford, which is one of the first regions in the U.K. to give the haemophilus influenzae B vaccine, and, again, it was started around 1990 in Oxford, and then there's a delay, as we saw in Finland, and then we see this rise in diabetes.

And, in the United States, probably the best diabetes registry is Pittsburgh, and we see that post introduction to haemophilus influenzae B vaccine in the zero to four year olds we see this more than doubling of the risk of diabetes.

Risk benefit, well in the Finnish study we saw that this early vaccine, the Connaught vaccine, which we were studying the PPRD, was associated with 58 cases of diabetes per 100,000. Now, if that vaccine were 100 percent effective, 100 percent effective, it is supposed to prevent seven deaths and brain damage

in seven of 26 kids. So, you can see that the adverse events, when we are looking at only one autoimmune disease, diabetes, is several fold greater than what the benefit is.

Now, again, the pneumococcal vaccine is really seven vaccines, so you could expect to see that the adverse reaction would go out significantly more and the benefit of the pneumococcal vaccine is expected to be less than the benefit of the haemophilus vaccine. So, the benefit would be substantially less.

Now, in the early PPRD vaccine which we studied, it was associated with about 58 cases of diabetes per 100,000. We have a birth cohort in the U.S. of about 4 million kids, if we immunized all the kids for a ten year period, ten birth cohorts, we'd expect an extra 24,000 cases of diabetes. Now, I said that we studied the PPRD, which was one of the first generation conjugated haemophilus vaccines, as the more potent second generation conjugated haemophilus influenzae B vaccines entered the market in Finland the extra risk of diabetes increased to about 100 cases per 100,000, so this would translate to about 40,000 children, extra cases of diabetes in this country, if we immunized ten birth cohorts.

Now, again, the pneumococcal vaccine is seven vaccines, so if we immunized ten birth cohorts we may have, in fact, an extra 280,000 cases of diabetes, that's a quarter of a million people, assuming that there was a direct correlation between one vaccine and seven vaccines. This is a tremendous risk to society.

Now, the Food and Drug Administration is guided by the U.S. laws, and the U.S. laws are written in Code of Federal Regulations, which say that vaccines must demonstrate safety before being put on the market. We've proved that the haemophilus influenzae B vaccine has never been demonstrated to be safe. We, in fact, proved that the pneumococcal vaccine, which you've heard about today, has not demonstrated safety either.

Now, Jean-Pierre Allain is a famous French, or infamous French public health official, who gave HIV positive blood products to hemophiliacs. He, and about three other public health officials, went to jail for this, for blatant disregard to the law.

From his actions, maybe 400 people have died. The issue is that when we are looking at giving the pneumococcal vaccine to everybody in the country, you know, all the children in the country, we are

looking at mortality that may exceed 250,000 individuals, so clearly it's potentially much worse than what Jean-Pierre Allain has done.

And, my last slide, one of the reasons the French were very upset with their public health officials was that, first of all, there were ways of testing blood products for the contamination of those viruses, and there were also ways of inactivating viruses in blood products. Well, the same way with vaccines, there are ways of testing vaccines for their ability to induce diabetes, as we discussed, and there are also ways in which vaccines can be given without increasing this risk, and this is just one possible mechanism, the CDC's own data showing that immunization starting in the first month of life is associated with a decreased risk of diabetes in both groups, both studies, two separate studies, compared to when the hepatitis B vaccine was given at eight weeks of life. So, this is just proof of point that, in fact, we don't need to just blindly give children vaccines and expect, well, we are preventing pneumococcus, we must be doing good things. In fact, if we take our time we can find ways of having both worlds, preventing infections, as well as not inducing the risk of autoimmunity.

That's all I have to say, thank you for the time. Any questions, I'd be more than happy to answer them.

CHAIR GREENBERG: Thank you, Doctor Classen.

For the record, can you identify your affiliation?

DOCTOR CLASSEN: I am President of Classen Immunotherapies.

CHAIR GREENBERG: Thank you.

We have another -well, first, are there any questions?

If not, we have out next — thank you very much, Doctor Classen — we have our next open hearing speaker, Ms. Newby.

MS. NEWBY: Hello.

Thank you for letting me speak today. My name is Carla Newby, and I serve as the General Manager for the Meningitis Foundation of America. I'm speaking today in support of this vaccination, not only on behalf of the Foundation, but also as a mother whose son died from pneumococcalmeningitis. One year and one week ago, October 28, 1998, I was forced to watch my youngest child, an only son, die from pneumococcal meningitis. Jacob passed away only one month before his 7th birthday.

As you well know, the only way to determine for sure if a patient has meningitis is to perform a spinal tap. That's a problem. Some doctors refuse to do spinal taps. At best, it seems the doctors often delay the order of a spinal tap. Either way, the necessary antibiotic treatment is often delayed. The tragic result is that children commonly suffer lifelong disabilities, or in the case of my son and many others die from this disease.

In my role at the Meningitis Foundation, I hear the same story over and over again from parents throughout the country, from parents who have had their young babies die from pneumococcal meningitis, as well as from parents of school-aged children and even young adults, the children who suffer this disease and the parents who bear the heartache for the rest of their lives are from all walks of life, rich, poor, middle class, all ages and all races.

My son Jacob was an all American kid. He had no special medical problems. He had none of the special conditions that would have made his doctor think that he should receive the existingpneumococcal vaccination, but he still got pneumococcal meningitis and we watched him die.

Prevention of pneumococcal disease is

clearly the answer to avoid these tragedies. The vaccination you are considering today offers promises of preventing pneumococcal disease in millions of children. The clinical trials have demonstrated how effective it can be in protecting children against the most serious forms of pneumococcal disease. I strongly urge you to support and approve this vaccination, and that you do everything possible to make it available to children as quickly as possible.

All of us have heard the complaints about the number of vaccines our children now receive. Maybe those people have complaints — have never experienced first hand the tragedy of a loved one suffering from a serious disease that could have been prevented from a vaccination. Believe me, none of us who understand the devastation pneumococcal disease can cause will ever complain about too many shots. We want to do everything humanly possible to prevent disease from destroying our children and our lives.

Pneumococcal disease is serious, deadly and crippling. We absolutely must do everything we can to prevent children from getting it. The hardest thing I've ever had to do was to tell my son it was okay to stop fighting and to let go. Please do everything possible to ensure that another parent never has to

say those words to their child.

Thank you for your time and attention.

CHAIR GREENBERG: Thank you, Ms. Newby.

Any questions?

Okay. I think we are going to move on, Doctor Pratt, to the — are there any other people in the audience who wish to make a statement? Okay.

What I think we should do is go through these one by one and sort of talk them through, and see what questions we have and how close to a consensus we have.

So, the first question is, do the data provide sufficient evidence of efficacy against invasive disease for Prevenar as it is studied in the efficacy trial, in as you know, two, four, six and 12 to 15 months, and if not, what additional information should be requested. So, the first question really is, one, do you think there's sufficient evidence of efficacy, and I'll take any comments the panelists want to make.

Doctor Ferrieri?

DOCTOR FERRIERI: I assume you'd like us to just open this up and then we can move on to more controversial questions, perhaps.

I think that the data provided were very

compelling in demonstrating efficacy against invasive disease against the pneumococcal serotypes in the vaccine given under the conditions of the efficacy trial.

CHAIR GREENBERG: Not a highly controversial statement in my mind.

Does anybody else on the panel have any other point of view? Many of you on this panel have, obviously, been engaged in vaccine trials, and it is rare for any of us to have 17 and zero numbers.

Dixie?

DOCTOR SNIDER: Well, I don't think this is a highly controversial question, but, perhaps, it is important to say that the evidence, of course, is very strong for protection against invasive disease caused by the vaccine serotypes. The issue of any cross protection against other serotypes is not very substantial at this time, and at this point it looks very good in the one northern California Kaiser study with regard to the lack of replacement, but, obviously, that is something of concern.

There is also the issue that I'm sure most people in the room, if not everybody in the room is aware of, and that is that we don't have the same serotypes around the world and, therefore, what data

are available for the U.S. at this particular time are not necessarily applicable to other countries and may not be applicable to the United States at some point in the future.

CHAIR GREENBERG: And, of course, what Dixie says is absolutely true, but it, in fact, is true about all existing vaccines as well, where there's always the possibility of change in the pathogen. That's one of the uncertainties that we have.

Any other comments?

Well, since there aren't, I'm going to now then simply poll the committee members. I'm open to more discussion of this, if there is any, but if there's not I'll start with you, Doctor Daum.

DOCTOR DAUM: I think this is a giant step forward for the health of children, and I vote yes on question one.

CHAIR GREENBERG: Doctor Kim?

DOCTOR KIM: Again, I guess this has been addressed by others, that this disease is certainly particularly invasive diseases due to pneumococci, namely, meningitis, is a very serious disease, with a considerable mortality and morbidity, based on the data presented today I will support the license of this product.

CHAIR GREENBERG: Doctor Snider?

DOCTOR SNIDER: Yes, the data are sufficient.

CHAIR GREENBERG: Doctor Stephens?

DOCTOR STEPHENS: This is an important breakthrough vaccine, and I think the data was compelling. I would add a couple of caveats. I think we haven't heard much about the efficacy of this vaccine in high-risk groups, which is an important area and subject. I think there are a number of unanswered questions regarding the efficacy, long-term efficacy of this vaccine, which have not been addressed. But, I think in essence my response is yes to question one.

CHAIR GREENBERG: Ms. Fisher?

MS. FISHER: I think the evidence is compelling that is protective against invasive disease. I wouldn't say it is compelling in terms of the other otitis media, et cetera, but that's not what we are considering today.

I would like to know more about mechanism, I'd like to know more about interference of maternal antibodies, but for question one only.

CHAIR GREENBERG: We are only dealing with question one at the moment for the rest of the people here.

Doctor Estes?

DOCTOR ESTES: I think the data was quite convincing, and my answer to this question is yes.

CHAIR GREENBERG: Doctor Hartigan?

DOCTOR HARTIGAN: I also think the data was convincing and my answer is yes.

CHAIR GREENBERG: Doctor Ferrieri?

DOCTOR FERRIERI: I'm very enthusiastic about licensure.

CHAIR GREENBERG: Doctor Glode?

DOCTOR GLODE: Yes, I think the data provide sufficient evidence for efficacy.

CHAIR GREENBERG: Doctor O'Brien?

DOCTOR O'BRIEN: Yes.

CHAIR GREENBERG: And, for the record, I also say yes, and would simply second my colleagues in saying that this seems to be an extremely exciting breakthrough for a disease that can have a devastating effect.

So, we'll move on to the next question then. Do the data provide sufficient evidence of safety of Prevenar, and, if not, what additional information should be requested? And, I'd like to hear some comments from the committee about safety. We've seen a fair amount of data, I would say it's complicated

data, and it's multi factorial and there's all sorts of analysis of it, so what are your thoughts and what further information do you want, and what do you think?

Doctor Snider?

DOCTOR SNIDER: Well, first of all, as we all know from recent experience with rotavirus, we never have sufficient evidence surrounding safety before we are in a position to be licensing vaccines. And so, it's important to continue to look at safety data after licensure to look for uncommon events.

Here, I think we really have a lot more data, though, on common events than often we have had, because, as was pointed out, of the place that this study was done and the kinds of record systems they have, and the kinds of research infrastructure they have and so forth. And so, if anything, I think there's more safety data here than we have gotten in the past.

As has been pointed out, there's some confounding here because of the fact that another — the control was another experimental vaccine. It was good to be able to see some of the vaccine safety data link data prior to the use of either one of the vaccines to let us know that some of those uncommon

events were in the ballpark of what were observed before. Otherwise, we wouldn't be able to say over an average two-year follow-up period that some of these things were not of concern, or had as much assurance about that.

I think the issue which was raised around diabetes, about long-term effects, is something we are all sensitized to, and we recognize the need to look properly at long-term events, potential long-term adverse consequences of vaccines. And, that's challenged not just with this vaccine, but for many other vaccines that are already licensed, as well as new ones that come before us.

So, I was not, with regard to safety, was not particularly surprised that when seven vaccines were given compared to one vaccine, in essence, that there were more local reactions or more systemic, but non-serious, reactions. And so, I felt that the safety profile given, particularly given comparisons to what has proven to be used in the past as a standard of care, such as DTP was actually let, the overall profile was better than whole cell DTP, given the fact that we were providing benefits against or protection against seven serotypes was a reasonable tradeoff with regard to safety. So, I personally was

comfortable with that.

But, that's, I think, additional information on that, on even the local reactions, would be useful to continue to collect.

CHAIR GREENBERG: Thank you, Dixie, for your usual good and well-balanced answer.

Any other comments on safety? Now, safety is a very important issue, remember you are always weighing safety and efficacy, and that's the issue that we are dealing with. Do we have any other — I'm just going to step in while the committee collects their thoughts and just say that I also just couldn't be happier with the venue where this trial took place, and the database and accessibility of being able to do multiple comparisons, and I think we should all just take our hats off to the Kaiser team that put this together, because they sure overwhelmed me. I have too many comparisons in my mind at the moment to really figure it all out, but there certainly is access to an awful lot of data, which I think sets the bar for future studies.

Any other questions about safety? If not, I am going to start over there in the right-hand corner again with my colleague, Doctor Daum.

DOCTOR DAUM: It was much better yesterday

morning when I sat up there.

I'm very comfortable with the safety profile data that I saw today that the safety and effectiveness ratio comes way down on the effectiveness side. I am mindful of Doctor Snider's comments, and agree with them, and believe that the long-term, post-marketing assessment needs to be in place. I believe it is in place. There are mechanisms for capturing these things, and that we might need to revisit this, but for right now I'm very enthusiastic, the short-term safety data we saw today were impressive, and this is a safe vaccine.

so, I think, yes, the evidence is sufficient.

Doctor Kim?

DOCTOR KIM: Well, I guess there's no absolute answer to this question, unless there is a continued monitoring of potential adverse effects or other unanticipated side effects that may occur following licenses. So, with that in mind, the data presented on localized systemic reactions appear not to differ from that we have seen with the other licensed vaccines. So, with that, I would support, the safety data appears to be, you know, acceptable.

CHAIR GREENBERG: Doctor Snider?

DOCTOR SNIDER: I think I've already answered it, but, yes, I think the data —

CHAIR GREENBERG: For the record.

DOCTOR SNIDER: — for the record, I think the data are sufficient on safety, as I already indicated. I think additional information should continue to be collected, as it relates to local and system reactions, but more importantly long-term events need to be evaluated using good scientific methodology, with attention to any confounding and to all of — hypotheses being met.

CHAIR GREENBERG: Doctor Stephens?

DOCTOR STEPHENS: You can never be sure about the long-term safety of any product, but I think the data do provide sufficient evidence for safety as we now view it.

CHAIR GREENBERG: Ms. Fisher?

MS. FISHER: There's not enough known about the safety of this vaccine, especially when U.S. data shows that local systemic and neurological reactions are more frequent in the pneumococcal vaccine group than in controls.

The fact that the whole cell DBT vaccine was used extensively in this trial, and an experimental meningococcal vaccine was used to control further

clouds the safety picture.

There is no biological mechanism data that has been presented to this committee regarding adverse events, and we don't know if the addition of this vaccine to the routine schedule will cause ultimately an increase in autoimmune or neurological disease in children and young adults.

The fact that the ACIP committee has recommended this vaccine for universal use in all children, before this vaccine has been licensed, is highly inappropriate, because it means that policymaking has preceded the scientific evaluation by this committee of this vaccine, and it means that when we vote for licensure we vote for basically mandatory use of this vaccine, because once a vaccine is recommended for universal use by ACIP it is put into the mandatory schedule.

And, this happened with rotavirus vaccine, and now with this vaccine, and I would hope that it would never happen again, because it does not instill confidence in the public in the integrity of the licensing process.

CHAIR GREENBERG: Doctor Estes?

DOCTOR ESTES: I share the words that have been said earlier in terms of the need for long-term

follow-up, but I think that the data that were presented today do provide good evidence of safety for this vaccine.

CHAIR GREENBERG: Doctor Hartigan?

DOCTOR HARTIGAN: The data seem to me to provide sufficient evidence, even though it was an experimental control, but long-term follow-up should be looked at.

CHAIR GREENBERG: Doctor Ferrieri?

DOCTOR FERRIERI: Well, I share other opinions here that have been stated by the majority, that the data presented certainly suggests that this is a safe vaccine. Anticipating questions from parents who want to know what might happen if my child gets the vaccine, and you might say, well, at the very least there may be — he has a very high chance of not having any side effects, on the other hand the worst scenario is that the patient, your little baby, may develop a very high fever, be listless, irritable, have a painful limb with diminished appetite, and might even need to be hospitalized. And, I use this example in order to stimulate conceivable studies that could be done to examine the possible beneficial value of non-steroidal anti-inflammatories given prior to complex vaccines like this, examining whether there's

any attenuation of immunogenicity.

I recollect seeing a small paper several years ago, perhaps, seven or eight years ago, not with the polysaccharide vaccines, but with routine DTWPE and, perhaps, something else showing certainly one can attenuate fever and other local side effects. And, I'd like to, as we move forward with the complexity possibility that we will even have a more expanded repertoire of this pneumococcal vaccine, then I think we are asking for more and more side effects, adverse events, not life threatening necessarily, but they can diminish the credibility and interest of parents in having their children vaccinated.

So, I think it's obligatory for us to examine whether there's a safe way of ameliorating some of these reactions.

CHAIR GREENBERG: Doctor Glode?

DOCTOR GLODE: Yes, I think the information presented this morning provides sufficient evidence of safety, again, with the caveat that events that would occur at a rate of one to 50,000 that would be serious we won't know about, except for very stringent and careful post-marketing surveillance. And, I don't know if things have changed and if there's currently a mechanism by which manufacturers are scheduled on a

regular basis to present post-licensing data, but I'm concerned about rare serious adverse reactions that occurred at a significant rate of one in 50,000, as well as the long-term follow-up for other chronic conditions.

CHAIR GREENBERG: Doctor O'Brien?

DOCTOR O'BRIEN: I think the data certainly were supportive of this vaccine being safe. I share Doctor Glode's caveat that we really do need to be sure that we look at potential adverse reactions. I'm less concerned, I know the rotavirus vaccine is being brought up as a concern rightly, but this is a different kind of vaccine, and the prototype more like it is the Hib vaccine, which has proven to be quite safe. So, I have more assurance on that basis.

CHAIR GREENBERG: For the record, I think also that safety has been demonstrated. I would simply like to say that it is a daunting task to ensure, in anyone's lifetime, that the long-term effect of a vaccine is totally understood. When you immunize a child, presumably you have a 70-year approximate time frame in which some adverse event could be associated with that vaccination. And, scientifically how to get at that is very, very hard. I think we all need to think about better ways to do it, but at the moment it

is a very — you have to weigh that with the fact that there are children dying frompneumococcal meningitis. And so, I feel that the preponderance of the data says this is safe, but I think we really need to think about how better to understand possible long-term consequences.

Can we have the next set of questions?

Well, here's the one where you really have a lot of interactions, so please discuss the data regarding concurrent use of Prevenar with other vaccines administered according to the recommended schedule of infants and childhood immunization. So, just to put this, you saw lots of data put up there with many interactions, and the question really is, do we know enough, or do we know sufficient amounts to say that this vaccine can now be incorporated into general use, and we feel comfortable that we are going to muck up what we currently have.

Dixie, so far you've just cut right to the chase. You are hot, do you want to continue?

DOCTOR SNIDER: Oh, so that's the reward I get.

CHAIR GREENBERG: Yes, never volunteer.

DOCTOR SNIDER: Well, I thought the data were somewhat concerning, mostly because there are a lot of

comparisons, and the type one polio is an example, or polio is an example, because the type one, responses to type one was lower, but then when I went back and looked the response to type three was higher. So, I don't know what to make out of that, and I was glad Karen made her comment, that with regard to the actual -- the absolute responses of the participants, there doesn't appear to be any reason for major concern. But, this clearly is an area, another area, where we need to continue to look at this, and I'm not sure whether the data are available or embedded in this study to tease more out, or whether additional studies need to be done.

But, overall, I'm reasonably sure that there are not any monsters in here, in terms of there being interference which would lead to an increased susceptibility to disease, but have some concerns because of the small amount of data and the lack of clinical endpoints, as opposed to immunologic endpoints.

So, I think it's something we need to continue to give some attention to.

with regard to the safety of the concurrent use, which is another issue, I think that we do have this confounding effect of, as has been pointed out in

shifting around from whole cell to acellular pertussis, there are also, with the confounding, trying to look in this trial — I mean, the ethical reasons for giving the other experimental vaccine were laudable, it's just that from a scientific standpoint it makes it a little bit more difficult to figure out what's going on. So, that confounding makes the data difficult to interpret, a little bit more difficult to interpret.

So, bottom line is, I think that what was outlined as appropriate concurrent administration is probably okay on a population basis, but I would like to see more data in the future on that.

CHAIR GREENBERG: Doctor Ferrieri?

DOCTOR FERRIERI: One of the questions that will be asked by primary care physicians is the influence on the haemophilus conjugate vaccine and its antibody responses, and the data that has been presented suggests that there may be some attenuation when the pneumococcal vaccine is given with DTaP and the haemophilus vaccine versus the control group without the pneumococcal, but the titers are still extremely favorable and eons beyond what one would need for protection against haemophilus influenzae type B. But, the numbers are small, and so I would

echo the need for expanding studies of this kind to examine responses to the other vaccines administered in any post-licensure phase.

And, the other point raised by someone else here earlier, I think, is an important one. We don't have the data we would like on other products, other than the HbOC, and so we know that many healthcare systems that contracts are put out that are based on price only, without consideration of compatibility of one vaccine with another or scientific medical rationale, but it's strictly bottom line contract. And so, I think careful thought must be given to this and studies done to demonstrate that there is no modification of either product in the face of some other haemophilus product, haemophilus conjugate.

CHAIR GREENBERG: Other comments? Doctor Daum?

DOCTOR DAUM: Thank you. I think that we haven't begun to deal with the probably more difficult part of this question, and that's what happens when combination vaccine research begins with the pneumococcal conjugate being a component of a putative new combination vaccines.

And, that might be a more difficult issue to deal with. We don't have data today to need to deal

with that, except that I would encourage the manufacturer to proceed with development and assessment of combination vaccines, including this new vaccine, as quickly as they are able in an effort to keep the number of injections down that children need to receive.

In terms of vaccine components given separately, one is always faced with a conundrum when one analyzes the data, because you can do a correction for multiple comparisons, and thereby make a demonstration of significance more stringent, but the price of that, of course, is to miss real comparisons which shook out at a less stringent level. So, I'm actually glad the data were presented the way they were today, so that we can discuss and assess all possible interactions and decide whether the statistically significant ones are clinically important.

My view is that most of these in combination vaccine research that I've done myself and seen others do, that many of these so-called significant interactions, in fact, represent alpha errors and don't hold up to repeated study.

And finally, although Doctor Ferrieri's point is correct, that the fourth dose had raised some

concerns about interactions with the Hib component, the primary series, the manufacturer now has data from two, and I think even three, trials, that the primary series, the Hib response was enhanced by children that received the pneumococcal vaccine at the same time. That raises the possibility of doing some investigation to see if the actual milligram dose of these vaccines could be turned down without loss of effectiveness or deterioration in safety and, perhaps, these vaccines could be made available to more children around the world.

CHAIR GREENBERG: Ms. Fisher?

MS. FISHER: We have been given no data about what occurs at the cellular molecular level when you give this vaccine in combination with all these other vaccines. If this vaccine were being licensed for use, voluntary use is one thing, but it's going to be inserted into the mandatory schedule, all children ostensibly are going to be receiving it, which means what we basically have here is a post-marketing experiment, and I think that we need to know more about the biology of what occurs in the human body when you give this vaccine in combination with other vaccines, versus just simply clinical observations.

CHAIR GREENBERG: Doctor O'Brien?

DOCTOR O'BRIEN: I'd just like to follow-up on the Hib question, and note that I never heard any mention of any cases of haemophilus influenzae disease at all, in either control or vaccine group, both of which got CRM-related products. Small scale, but if there was some problem we might have seen a case or two. Was there any?

CHAIR GREENBERG: Doctor Black is going to address that issue.

DOCTOR BLACK: We have not had a single case of Hib disease since 1991, both before the trial and during the trial.

CHAIR GREENBERG: Doctor Glode?

DOCTOR GLODE: I was just going to say that I continue to be impressed as new vaccines are being studied with some unexpected immunologic outcomes that seem to happen in many vaccine trials, and I think this is one of them. And so, with the Hib antibody response being enhanced with the early doses, but suppressed with the later doses, that still is disturbing to me. And, although I accept Doctor Siber's possible immunologic explanation for it, I think we could have support for that by studying some of the other Hib conjugates and, perhaps, shed a little light on that issue.

And, I am concerned as new combination vaccines are licensed, et cetera, that it will be very important to study this vaccine, because I just think some of these interactions do seem a little bit unpredictable and surprising us, and then we learn about it and can explain it.

CHAIR GREENBERG: Doctor Stephens?

DOCTOR STEPHENS: One issue that I'd like to address is the catch-up schedule which we haven't talked about very much. In the data from the catch-up schedule, and it's not on our questions, so I'm not sure that we are being asked to judge that or not, but, you know, the data as I saw it was very preliminary, or the numbers were much smaller for the catch-up schedule and it seemed less defined. And, certainly regarding question three, the potential interactions with other vaccines in the catch-up schedule, I think have not been addressed.

And, just as a general comment, and I think I agree with most of the other comments that have been made, the issue of overall vaccine delivery and the issue of continued increasing antigen load in children, and the desire to look at development of alternative vaccine delivery systems.

CHAIR GREENBERG: I'm just going to make a

comment here. I think it was the manufacturer who mentioned the fact that attempts to study comparisons of various vaccines were looked upon as somewhat low level types of research for the VTUs, or at least somebody mentioned that the VTUs felt that the mundane questions of how to study multiple vaccine interactions was not appropriate for good scientists.

And, I would simply say that this committee seems to be daunted with this question on almost ever vaccine, and I personally would say that it's a perfectly good thing to use the VTUs for, so our colleagues in the audience who are NIH and who have oversight on the VTUs, those tremendous assets represent one of the few places where you can really do comparisons here that are very, very hard to do in other ways, and I would suggest that people start thinking about that as one of the places to do research.

Any other — just a little editorial, that was just an editorial — any other comments?

Bill?

DOCTOR EGAN: Doctor Egan from FDA.

I forget the data exactly, but, perhaps, either the manufacturer or Kaiser could comment on the response to the Hib vaccine that was done from the

initial trial, particularly, with regard to the percentage of seroconverters at the various levels, relative to the data that's presented now for the pneumococcal arm.

CHAIR GREENBERG: I'm not sure they understand your — am I correct that the manufacturers aren't understanding the question? They are looking puzzled over there.

DOCTOR EGAN: Yes, I'm sorry, there was some concern about in the pneumococcal arm about the GMCs, the titers going down after dose four, and the percent of seroresponders, the 97 and 98 percent in the pneumococcal arm, do you recall what those numbers were from the initial study of the haemophilus vaccine?

DOCTOR SIBER: You're really asking, Doctor Egan, from the original efficacy trials done at Kaiser?

DOCTOR EGAN: Yes, that's correct.

DOCTOR SIBER: Those are not data we brought. The best we can do is the control comparison in the one study that was controlled, which just suggested I think it was about 20 micrograms per ML. Does anyone in this group have a solid memory that's worthy of putting up here on the initial trials? No? Well,

those are the data we are talking about right now, we are talking about in the control trial. Wait a minute. The question is, the original efficacy trial done at kaiser with HbOC, what were the levels with boosting in those trials, and the answer is, we would have to get back to you on that.

Dot says Midori's memory, and she has vouched for a pretty good memory, is 16 to 22 micrograms geometric means, in the good old days.

CHAIR GREENBERG: Say it again, George.

DOCTOR SIBER: In the Kaiser study itself, the immunogenicity was done as part of the Hib efficacy trial, we were asked what the geometric mean antibody response was after the booster dose, and the memory of our staff, it is between 16 and 22 micrograms, but I would ask you to let us get back to you to confirm this, because this is memory.

DOCTOR EGAN: Yes, and the percentage at greater than one microgram. My recollection is that these numbers here are actually higher.

DOCTOR SIBER: Forty-five might be a record.

CHAIR GREENBERG: Okay.

I have the request to make a comment from Doctor McInness from NIAID.

DOCTOR McINNESS: Doctor Greenberg, your

editorializing forced me to my feet. I'm puzzled by the comment that the VTU investigators sometimes are scientifically non-challenging. In fact, I think for the record we have been involved in a variety of relatively extensive trials looking at what we call mix and match combinations, and I don't believe that philosophy has changed in our partnering to find effective and safe vaccines.

So, I would extend my invitation earlier this morning to have some discussions on what might be possible in that framework. Thank you.

CHAIR GREENBERG: Well, that's the best possible outcome, and to the degree that I misinterpreted or misheard what was said earlier, I'm happy because that's a terrific thing, and we really need the VTUs to address this issue, because it's an important one.

Anymore — Doctor Ferrieri?

DOCTOR FERRIERI: I have a question for the sponsors, if they have any preliminary information from study 124-501 on the effect of the 9-valent vaccine on nasopharyngeal colonization with pneumococci, is there anything that we're learning from that that would influence post-marketing studies of the 7-valent vaccine in terms of addressing the

issue of the colonization, for example, with serotypes that are not in the vaccine, or the most basic question, does it influence nasopharyngeal colonization as Hib conjugate did for HIV?

DOCTOR SIBER: There are data published by Ron Dagan on this from a study in Israeli daycare centers, in which a majority of the children were enrolled into studies were they were randomized to either pneumococcal 9-valent vaccine or meningococcal c vaccine.

What the study showed was a variable reduction in the vaccine serotype, but the average was on the order of 40 or 45 percent, as I recollect, and that occurred rather quickly after immunization. These were toddlers at one or two doses of vaccine.

And, a more gradual increase in the vaccine recipients of non-vaccine serotypes, there's been lots of debate about whether that increase represents unmasking of non-vaccine serotypes, because we eliminated the vaccine serotypes, whether they are there in similar concentrations that were simply allowed to be cultured when you got rid of the dominant vaccine types, and that is not yet resolved.

Another effect that was observed is that the character of the antibiotic resistant stains was

significantly reduced in children who got the pneumococcal vaccine.

There will be additional data which are not yet available that look at overall antibiotic use in that daycare center population, and overall morbidity in terms of doctors visits, otitis, and so forth, that are shaping up to be interesting, but they have not yet been presented by Doctor Dagan.

CHAIR GREENBERG: Doctor Pratt, do you feel you are getting a good answer here, since you don't have a specific question I'm not sure you are getting a discussion. Are you becoming informed on number three?

DOCTOR PRATT: Yes, I find the discussion useful.

CHAIR GREENBERG: Any other — I think I have a good idea so far — did I see another hand over here — of where the panel — anymore data for number three?

DOCTOR ESTES: I was on to four, I'm sorry, Harry, I didn't realize we were through with number three.

CHAIR GREENBERG: Well, we are not quite yet, until everybody gives me the high sign that they think they are done with talking about three. I think we are pretty done on three, so let's go on to four, and

this is good, I think we are making good progress.

Please identify any issues that should be addressed in post-marketing studies. Now, of course, we've touched on a bunch of this, but I won't -Dixie, I've trained him here, Dixie, I'll let you go first.

DOCTOR SNIDER: Well, since you called on me last time, I thought I'd just volunteer this time.

Yes, a number of things we've already mentioned. We've mentioned safety, particularly, long-term safety issues. I think a number of us are still concerned about the concurrent administration issue, and we'd like to see more data on that. Mention has been made about efficacy and safety, but particularly efficacy in other risk populations that were not included here. Certainly, there are other health outcome data, notably pneumonia, that we haven't seen data on yet, so somewhere along the way we'd want to look at that. And, probably post-marketing it would be -- even if you do it in a trial, this might be the way to really figure out how much pneumonia is due to these serotypes, and how much acute otitis media, for that matter.

We need to follow the serotypes, both in terms of the replacement issue and in terms of the vaccine serotypes that might be showing up. I think

it was some suggestion in 19f, I believe, that, you know, it may mean nothing, but the question is whether the current vaccine needs to be beefed up in any way to protect against any of the vaccine serotypes.

The issue of catch-up has been mentioned and the proper dosing there, and I think we could open it up even further and say, how many doses, and when, we really don't know, and there is suggestion from the data, as has been commented on, that you might get quite a bit of efficacy out of one initial dose in the series, but obviously we don't know how long that might persist.

So, it will be interesting over time to look at pneumococcal conjugate vaccines to try to ascertain what — how many doses you actually need and what is the optimum interval between doses. So, I think those are some of the things down the road we'd be looking at, not necessarily all of them that the manufacturing are doing, but these are some of the things that come to mind.

CHAIR GREENBERG: Doctor Kim?

DOCTOR KIM: You know, this is, I think, a serious — again, this is pretty much bottom line, but it is very, to me, important to document that invasive pneumococcal disease is, indeed, decreased and

maintained throughout, you know, the coming years, make sure that there's no — not only replacement with other serotypes, you know, or replacement by other pathogens in the community regarding invasive disease.

And, an additional comment, I think that needs to be done, which we touched several occasions, I mean, is regarding some of the immunologic profiles and the assay issues, and I think it is important to have some sort of a consensus or guidance from the FDA regarding the issues about protective levels of antibodies, which, you know, may differ depending upon the types of diseases, like invasive disease versus — again, I'm not still clear about the beneficial effect of this vaccine against otitis media, for example, and I think those types of issues continue to be very critically analyzed through the samples are variable from participants, I think those are extremely, to me, valuable resource to address some of those issues.

And, again, as you know, the assays ought to have some variations, so that if you are looking to some numbers, and those numbers happen to be within two-fold, I'm not sure I have any confidence in those numbers in providing some guidance to, let's say, second, third generation vaccines to, you know, imply that those vaccines are, indeed, efficacious or not.

CHAIR GREENBERG: Ms. Fisher, then Doctor Daum.

MS. FISHER: I have a practical question. If this vaccine is licensed and shortly put out on the market for use in all children, how is the FDA and the CDC, how are they going to determine when a child suffers this healthproblem following vaccination with this vaccine, in combination with all these other vaccines, if it is indeed due to the pneumococcal vaccine?

CHAIR GREENBERG: Well, I don't think there's — perhaps, there is somebody here who can speak for the CDC, but that's a question directed at the FDA first.

MS. FISHER: Well, Dixie is from CDC.

CHAIR GREENBERG: Yes — no, no, but I'm letting the FDA, since this is an FDA meeting, take first chair in this response.

DOCTOR GOLDENTHAL: Thank you.

Well, I mean, that's a very — you know, that's a very complex — you know, it's a very difficult question to answer, because when you are giving multiple immunizations attributing cause to one particular vaccine, or even to vaccination at all, can be difficult. I mean, we have a staff that's focused

on post-marketing evaluations, and looking at VAERS data, and looking for trends or any troubling findings that may occur. I think that a specific post-marketing study in the right setting may also be helpful to look for any unanticipated, you know, events, and maybe also detect any increase compared to background.

But, you know, in a setting of a non-randomized evaluation, that can be difficult to do.

MS. FISHER: I mean in any given case, you know, a parent takes a child in, and the child suffers a seizure, or suffers high-pitched screaming, or whatever, I mean, it seems that we need to have a clear idea if we are going to attribute that to the vaccine or not, and it seems that biological mechanism work is the only way we are going to get at that.

CHAIR GREENBERG: Dixie, and then Doctor Ferrieri.

DOCTOR SNIDER: Well, with regard to looking at vaccine safety, I think people are aware that we do have the Bayer system and people hopefully are also aware of the limitations of that system. Nevertheless, I think FDA and CDC, who work together with that system, would like to enhance it and make it better, and increase the participation in it among

clinicians and parents.

There are also the large link databases, such as the vaccine safety data link, which we would very much like to get the resources to expand, because people, I'm sure, are aware of the fact that your ability to detect rare events increases as your sample size increases, and, therefore, we'd like to include other organizations in the vaccine safety data link.

I think it's hard to get very specific about what one might do, depending upon — because it will depend upon what kind of event you are talking about, certainly all the events we look at we have to look at what is the temporal association, what is the biologic plausibility. At times one can do special case control studies to evaluate putative adverse events, at other times it does take a special study set up prospectively to be able to adequately answer certain questions.

And, as many people know, we are engaged in establishing a number of studies, both retrospective studies, nested case control studies, and prospective studies, to look at several putative associations between vaccines and various adverse events.

CHAIR GREENBERG: Doctor Ferrieri?

DOCTOR FERRIERI: I'd like to address the

issue of post-licensure bacteriological monitoring of pneumococcal isolates and present the fact that many academic institutions, many hospitals, medical centers, including university hospitals, do not routinely serotype pneumococci. And so, who will be responsible for seeing that they are examined properly, that they don't die in route? Will there be a central bank to receive them, and will that be organized somehow?

So, I guess I would appreciate any comment from FDA, CDC or the sponsor about this. We don't want misleading information, and we do extensive pneumococcal typing in the laboratory I direct, but there are pitfalls in doing this, and one needs to be aware of that.

So, I think this is really important as we move forward, to understand the full protection or cross protection, et cetera.

CHAIR GREENBERG: Doctor Pratt or Doctor Frasch, are you going to take a crack at that, at answering that?

DOCTOR SNIDER: Well, Harry, I'd be glad to say, I mean, I think CDC plans to continue the ABC data collection that George showed, and certainly that would be one source for us to be able to continue to

look at serotypes.

CHAIR GREENBERG: Does the sponsor have anything to add here?

DOCTOR FERRIERI: It's a lot different in doing this for a study and doing it under very diffuse conditions with all comers, and what will be the practice? Will FDA write something up, so that all physicians know that there's interest in examining those isolates?

CHAIR GREENBERG: Doctor —

DOCTOR FERRIERI: Carl, what do you think about that? How do we make it not a problem?

DOCTOR FRASCH: Well, I think it's FDA's job to license, and then monitor the safety through the VAERS system, but I think it's the CDC's job to do the strain surveillance, you know, through Doctor Fraklan's lab and so on.

CHAIR GREENBERG: Doctor Daum, and then Doctor Stephens.

DOCTOR DAUM: Just to add a couple of things, and try not to be repetitious to things that have been said before. I think we need some studies directed at the performance of this vaccine in high-risk groups, specifically, sickle cell anemia patients and children infected with HIV, perhaps, asplenics. I'm sure there

are others that come to mind, but we need to know, need to be reassured that there can be bridging.

CHAIR GREENBERG: It was my impression that the manufacturer did show us a list of a fair number of immuno — of high-risk groups that studies were ongoing, which we'll need to see that data, but I think those studies, or at least we saw a slide that said they were underway.

DOCTOR DAUM: Also, I think that the duration of the antibody response, which has been touched on, is an extremely important issue, because pneumococcal disease differs quite markedly from Hib, which has been analogous so far, and that pneumococcal disease also is a problem in adults. And, it will be interesting to consider, at least, how long protection from a four dose series in early childhood can, in fact, endure, and how long is it capable of being boosted.

So, I would like to conceive and have performed some studies to look at that.

We also need to think about a vaccine that will protect against all cases of pneumococcal invasive disease, not just the percentage that we have captured in a 7 or 9-valent vaccine. There may be some carrier priming and carrier immunity issues here

that need to be explored and addressed, but buoyed up by the success of this first generation vaccine it might be fun to push that along as quickly as we can so the children aren't getting any pneumococcal invasive disease.

I also touched on before, but would like to just reiterate under the umbrella of question four, that I think the vaccine community needs to explore issues of bridging to other pneumococcal conjugates as quickly as we can, because I think that there may be other candidates out there that may be useful, and we won't know how to assess them.

I also will take up a theme that I touched on this morning in talking about post-marketing immunogenicity assessment. I don't know quite who should do it. I don't know what umbrella it should be done under, but I think that there should be some monitoring of the immunogenicity of randomly chosen lots that are put on the market to ensure performance is as good as it has been.

And, lastly, this issue of carriage with respect to vaccine, which has been well documented and incredibly complete in some populations, and clearly in other high-risk populations been much less complete in terms of eradication, needs to be studied more.

And, I would encourage people who are doing research in this area to pursue this, I think it's a very important issue.

CHAIR GREENBERG: Doctor Ferrieri, and I would encourage committee members now to really try to touch on things that haven't been said before, so that we can give the FDA as broad a list as possible. I think they've gotten a fair amount of input from us.

DOCTOR FERRIERI: As we're winding down, I feel it's very important to say something that FDA will not be able to control, but that has to do with allocation of resources and social policy. I understand that this vaccine is going to be quite expensive per dose, and I want us to mobilize as a group of physicians and scientists to see that this, as well as other critical vaccines, are distributed to disadvantaged, economically disadvantaged, disenfranchised racial minorities, in particular, who are at highest risk of invasive disease. And, as a single individual I can't do anything about this, but I think we should reflect on this and see that there is appropriate use so that the kids of Bethesda and Chevy Chase are not the only ones in Maryland who receive this vaccine.

So, what about inner city kids in Baltimore,

Atlanta, New York City, Chicago, et cetera.

CHAIR GREENBERG: And, I would just echo that, I assume that there are outer city kids in Bangladesh who sorely need this vaccine as well, and they are even further from it.

Doctor Snider?

DOCTOR SNIDER: I just wanted to respond to that. I mean, I just want to call to people's attention that actually we have a very peculiar situation in the U.S. with regard to that. If the vaccine is licensed and the ACIP votes to include the vaccine in the vaccine for children program, there will be a mechanism for purchasing the vaccine for the poorest children. Presumably, the richest will be able to purchase it as well, and it's those in the middle that are most likely to be deprived of the vaccine, or have the most difficulty obtaining the vaccine. And, it's just an anomaly of our vaccine delivery system these days, as to who is most likely to have difficulty obtaining it, and not the poorest of the poor.

CHAIR GREENBERG: Well, we have a big list of things that you folks at the FDA, and the manufacturer, and the CDC have to do, and Doctor Stephens is going to add to that.

DOCTOR STEPHENS: At the risk of prolonging this a little bit, I had seven categories, most of which have been covered. I do want to make a couple of points. One is an issue we haven't talked about, is individuals who may have received prior pneumococcalpolysaccharide vaccine, and the potential effects or interference effects of that vaccine on this vaccine, an area that we haven't touched upon, but certainly for high-risk groups that's an area of some concern, given other data and other systems suggesting that there may not be — there may be less of a response in those particular individuals.

The other has to do with as an adult infectious disease individual, there is a clear need for this vaccine or a much improved vaccine in the adult population, in terms of the immunocompromised patients with serious pneumococcal disease, and certainly in the elderly, and I realize those studies are ongoing, but it's an area of immense concern for many of us.

And lastly, an issue regarding, I participate as one of the sites for the ABCs, the CDC ABCs, and certainly those sites are ideal for looking at the impact of the introduction of a new vaccine. We certainly saw the dramatic decrease in haemophilus

influenzae B with the introduction of the vaccine in the Atlanta community, and I think it's important to document the introduction of this vaccine in sites where there is very good active population-based surveillance, to look at overall efficacy, and to identify potential effects on herd immunity, which was certainly a major benefit of the haemophilus influenzae vaccine that we really didn't anticipate when we began the studies.

CHAIR GREENBERG: Ms. Fisher?

MS. FISHER: I think also in any post-marketing surveillance there has to be attention paid over the long term to the increases in — possible increases in diabetes and other autoimmune disorders, asthma, with the addition of this vaccine to the routine schedule.

CHAIR GREENBERG: I'm just going to take a second here to underline what Ms. Fisher said, and I think it's clearly time for the vaccine community to really figure out the scientific way how to deal with these long-term questions that are so hard scientifically to deal with, and to develop systems so that we can be ahead of the curve as opposed to behind the curve, in having databases that are robust that really enable us to answer these questions.

And, I think my advice to the FDA and the CDC is, perhaps, and maybe it's already in place and I'm unaware of it, but it seems to me that there are real statistical problems and database problems, and all sorts of -- yes, and money problems, excuse me, that deal with this.

On the other hand, being behind the cure also creates money problems, and it seems to me that it might be a good idea for people to come together and say, what is the best solution we can come up with now, and start instituting it so that, otherwise five years from now, and ten years from now, we're going to have the same questions, and they are going to be very difficult to answer, because we won't have good databases. So, that would be, again, just editorializing.

Carl, I'm about to wind this down now, so make it brief.

DOCTOR FRASCH: I think I need to point out that Doctor Daum had made comments about not getting behind the game, shall we say, we've already had meetings regarding, through the WHO mechanism, one, how to get the pneumococcal conjugate vaccine out to the underprivileged countries. We've met there this year. We've already had another meeting regarding

assay standardization and possible mechanisms to allow for a second pneumococcal conjugate vaccine or an improved pneumococcal conjugate vaccine, so we are not exactly playing too much catch up.

CHAIR GREENBERG: That's heartening.

If there are no other new comments from the committee, I'd like to ask Doctor Pratt, do you feel you've gotten a full airing of the two last issues for which there wasn't real questions?

DOCTOR PRATT: Yes.

CHAIR GREENBERG: Okay, and the manufacturers, I hope, have been taking notes.

Okay. I'd like to thank the committee for being extremely active, and thoughtful, and also timely, and I'd like to thank the audience, and I'm going to call this meeting — oh, there's an open public meeting, does anybody want to address the panel before I close the meeting? Excuse me.

DOCTOR CLASSEN: Yes, I have one question.

Ms. Fisher brought this up, again, you know, do we have specifics on a plan of action to look at the effect of vaccines on diabetes? I mean, we heard about, Doctor Black brought up that they had historical data on diabetes, but I think three or four different vaccines have changed since that time, the

timing of the hepatitis B vaccine using the acellular pertussis vaccine versus the whole cell pertussis vaccine. There is other changes as well.

So, it's very difficult using the Kaiser database to look at the effect of vaccines on diabetes, and I was wondering if the FDA had some plan or specifics, that I guess Ms. Fisher alluded to.

CHAIR GREENBERG: So, any FDA —

EXECUTIVE SECRETARY CHERRY: This is not the time for questioning.

CHAIR GREENBERG: Okay, so we take that, the questions are over, I think the FDA has heard you, that they are well advised to have a specific plan to look at type one diabetes, and I hope the FDA is listening to me. These questions will not go away until the FDA generates — the FDA, government or whoever, generates compelling data to show that there's not a risk. So, I think it's important to get those databases in place.

Thank you, everybody.

(Whereupon, the meeting was concluded at 2:23 p.m.1

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/PHS/CBER

Date: November 5, 1999

Place: Bethesda, MD

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