Committee members that anything left on the tables tonight, in the way of paper, will be shredded, gone by tomorrow morning. So please, if it's important to you, take it with you as is appropriate.

I'd like to move now to discussion point two. We are not going to have a Committee vote on discussion point two because there are outstanding manufacturing issues that need to be addressed before it's appropriate for this Committee to do that.

However, we are going to have the same kind and Committee members willing, the same quality discussion that we would have, were we to bring this matter to a vote at the end.

So I'd like to begin with some general comments on this question as the Committee wishes and then we'll begin focusing each member to make a comment. General comments and discussion point two which Nancy has given me body english we should maybe read it.

The following discussion points pertain to safety. Please discuss whether there are, whether available clinical data are adequate to demonstrate the safety of this combination vaccine we're asked to comment on today, when given to infants at a primary series of 2, 4, 6 months of age are adequate?

I paraphrased a little bit but I think I got it right. Please comment on the increased rates of fever in infants receiving this combination vaccine. And then, again, if you're feeling is that the data are not adequate, what additional information should be requested?

So I'll have general comments first and Steve, I see you're getting into the habit of jumping into the abyss here.

DR. KOHL: Take Dixie's spot. The biggest concern I have is fever. I think it's real. I think the FDA has helped me because I think it's real and it's not trivial. We see fever that is increased both at the lower range and also at the intermediate range to the point where fever of a 101, and 101.5, I believe it was, or greater, is increased by about five percent.

That may not sound trivial but if this is a vaccine that's going to be widely used which I would anticipate it would, we're talking about four million kids a year, roughly, that's about 200,000 extra kids a year who are going to have a significant fever.

If a large proportion of those children are in that first month of life, say at four weeks, some of those, and I think a fair number of those, are

going to translate to sepsis work ups. Because that in this country I think is still a standard of care.

So I am, I'm quite concerned about that. I'm also concerned, as I mentioned, that the data for seizures are just not solid enough because of the zero in the control group. It was seven in the vaccine group and zero in the control group. And I would like to see more data on seizures to be assured that there's not an increased risk for seizure activity in children receiving this vaccine.

CHAIRMAN DAUM: Thank you very much. We're not necessarily going in order. So anybody that wants to jump in can do so. But we will hear from everybody before we're done. Ms. Fisher.

MS. LOE FISHER: Is it too late to ask the manufacturer a question?

CHAIRMAN DAUM: No, I don't think so. As it pertains to the statement on the screen.

MS. LOE FISHER: Yes.

CHAIRMAN DAUM: No, please, go ahead.

MS. LOE FISHER: During the trials, after which adverse events did you discontinue vaccinating with the combination vaccine and was the same criteria used in control arms?

And the second part of that question is,

when a vaccine adverse event occurs with the combination vaccine, do you have any idea which component is responsible, which of course is relevant in terms of contraindications to continue vaccination after an adverse event occurs?

CHAIRMAN DAUM: Thank you, Dr. Howe?

DR. HOWE: Let me just make sure I understand your first question. You're asking in the context of the clinical trial for what type of adverse event would you intentionally discontinue vaccinating the child?

MS. LOE FISHER: Did you discontinue? Did you decide you were not going continue to vaccinate? They dropped out, then?

DR. HOWE: In the clinical trials, the typical type of precautions for further vaccination were specified in the protocol, which means hypersensitivity reactions, allergic reactions to any previous dose.

The precautions to DTP-whole cell, which apply to DTPa as well would also be precautions to further vaccination and those children could have been withdrawn. But other than that, there were no other mandates for withdrawing or discontinuing a child from continuing in the trial. The usual practice.

MS. LOE FISHER: Well, I want to be real specific about this. I think it's important in terms of the outcome of the trial. So, children in the trial who had high fevers, over 103, over 105?

DR. HOWE: It is 40.5, I believe.

MS. LOE FISHER: Children who had high pitched screaming or unusual crying?

DR. HOWE: Yes. Seizures.

MS. LOE FISHER: What about seizures? What about restlessness?

DR. HOWE: No.

MS. LOE FISHER: So it was basically three things. It would have been --

DR. HOWE: As well anaphylaxis, obviously to the previous dose.

MS. LOE FISHER: Anaphylaxis, but you didn't have that in there.

DR. HOWE: Right.

MS. LOE FISHER: And then, do you have, did you have any idea which component was involved and what would you consider a contraindication? Would it just be those three reactions?

DR. HOWE: I mean the contra, first of all we wouldn't know in a combination vaccine exactly which component would be causing an adverse event.

However, if there was an adverse event explained or reasonably associated with a component of the vaccine based on historical data, such as for pertussis, one might presume that an AE such as that would be related to that component. But we don't really know when an AE occurs which component to attribute it to.

MS. LOE FISHER: So with the combo you'd basically want to, if an event occurred, you'd have to not vaccinate with any of the components.

DR. HOWE: Well if a contraindication to further pertussis vaccination occurred with the combo, you would stop vaccinating with this combo.

CHAIRMAN DAUM: Okay.

DR. HOWE: Whereas if an anaphylactic reaction, after the combination occurred, you would stop vaccinating with the combo.

CHAIRMAN DAUM: I think with respect to the discussion point, we've got the information we need on this question. Can we move on to other Committee comments about this discussion point. Dr. Stephens? Dr. Gerber next.

DR. STEPHENS: You were kind enough to provide us with data, I mean immunogenicity data on 027. Can you share any reactogenicity data on 027?

DR. HOWE: Yes, I have information on, do

you have the slide for fever? So, again, this study involved nearly, well actually a thousand subjects who received the DTPA-HepB-IPV mixed with Hib, given at 2, 4, 6 in U.S. infants as compared to separate injections of Infanrix, Engerix, Hib and Oral Polio.

This shows the fever rates in the study. You can see for the lower cut off rates those who received the combined vaccine, forty-two percent had a fever greater than or equal to 104.4 degrees versus 38.4 in those who received separate injections. And once again for the higher cut off the rate was lower, 2.2 versus 1.4.

CHAIRMAN DAUM: Thank you. Dr. Gerber.

DR. GERBER: I wanted to echo Steve Kohl's concern about the increased incidence in fever, particularly in the youngest of the infants and also my concern about extrapolating from what is primarily a German experience with respect to the clinical implications of this increased incidence of fever.

Although we're told that German physicians' approach to fever in infants is essentially the same as physicians in this country, looking at the use of antipyretics, there was some data about the very substantial use of antipyretics, routine antipyretics in this country compared to

Germany.

That would to me suggest that the approach to fever, that the feelings about fever, in this country might very well be quite different from Germany. And so I would very much like to see data in this country as to the actual clinical implications of this increased incidence in fever.

CHAIRMAN DAUM: Okay, thank you Dr. Gerber. Other comments. Dr. Diaz, please.

DR. DIAZ: I, likewise, am somewhat concerned about the increase in fever and yet I don't know enough about how that increase in fever translates into the end point of the, of disease prevention.

And I might step back by making a comment. I think in the manufacturer's package they comment for safety overall. I think there were about 6,900 plus children who had at least turned in one sheet regarding some safety measures and that about 5,300 of those were eligible for the analysis according to protocol.

So there were about 1,600 plus children that weren't overall in studies combined able to be analyzed in terms of safety and it's, they were excluded, I believe, at least the wording was due to

a departure from the visit schedule according to pre-specified criteria. So what I was trying, I see people shaking their heads. Is that incorrect?

DR. HOWE: The vast majority of the children that were excluded from the ATP analysis for safety were in study 011 and the reason was because in study 011, if you recall, it was originally an uncontrolled study with respect to U.S. license separate injections and there were approximately 1,600 infants who were enrolled prior to the amendment which allowed for the introduction of the relevant control group, the U.S. license separate administration group.

So in terms of a controlled comparison, it was felt invalid to include those first 1,600 children in the ATP analysis. However, we did an ITT analysis which does include all of those children and those data, the ITT analysis, were actually in the FDA's briefing document. And the conclusions are the same.

Furthermore, with all of the more significant adverse events that we're talking about such as the SAEs, seizures, what not, we're certainly talking about the ITT cohorts. So we're taking all of the children into account.

DR. DIAZ: Right. Thanks for clarifying that. Because that was my concern was the intent to

treat and the issue of how much of the fever may have played into children not finishing the series per se. But it sounds like that was not the issue.

DR. HOWE: Yes. And the seven thousand twenty-eight children, the overall database includes those 1,600.

DR. DIAZ: Okay. That having been said, I feel a little bit more reassured about that, that aspect. Back to the fever, overall, I think, I still don't feel that there's enough information in terms how much that additional fever translates into, for instance, physicians visits, perhaps sepsis work ups, hospitalizations, etcetera and whether that will really play into issues of further safety associated with the vaccine.

The fever, slight increase in fever, in and of itself, may not be an issue. It's just that I don't feel that I have enough information from the studies to date to say how that increase in fever translates into the overall care of the child during that episode. I'd like to see more information.

CHAIRMAN DAUM: Thank you. Other comments from the Committee. I'd really would like to hear from everyone about this. Dr. Fleming then Dr. Wharton. Dr. Wharton, then Dr. Fleming?

DR. WHARTON: Well, it was very interesting to see the information that was just put up on the board from the 027 trial. Where the, if I interpreted this correctly, the rate of fever in the standard U.S. licensed vaccine group was I believe thirty-eight percent compared to I believe forty-one percent in the other group.

Which is not a striking difference in, and it's much less striking than the data we have been provided from study 011 and 015 where we had rates in the twenties compared to rates of forty or forty-one. So that's interesting. I too am concerned about the prevalence of fever in these studies.

While my impression is that these fevers are at least in the trials to date have been largely benign and the incidence of high fevers has been much lower, it still is of concern and I share others concern about the, it precipitating sepsis work ups in very young children.

There isn't, given that when this vaccine is licensed it will be given as part of the recommended childhood immunization schedule, though, I am concerned about concomitant administration with Prevnar, which has also been associated with fever at least by my interpretation of the data provided in the

package insert.

With fever reported from thirty-three, in thirty-three percent of recipients of dose one to up to forty-one percent for dose three and forty-two percent for dose four.

And I don't know if these are going to be additive or multiplicative or what interaction is going to be between those two vaccines and I'm quite concerned about that. And believe that additional data are needed addressing that issue.

CHAIRMAN DAUM: So yours is a safety issue to do with the simultaneous administration of Prevnar. Okay thank you. Dr. Fleming.

DR. FLEMING: I think my thoughts are quite consistent with what many others have already indicated. My sense is that the data we have on safety and the sponsor has really focused in particular on the studies 015 and 011, provide us important insights about what, as they refer to the common AEs. The AEs that would occur at least as frequently or more frequently than one per one hundred.

Or it may be the only limitation to that insight is the vast majority of that data comes from 011 which is not only in Germany but with a different

schedule than what we would be looking at here. I am struck, though, at the level of consistency across the studies, not only the 015 and the 011 but the 003 and the 027.

They all show patterns of increases anywhere from the most modest which is 027, about a ten percent increase, to the 015 and 011 trials that show more on the order of a fifty percent or more increase in fever.

What's interesting is if you look at 39.5, then those four studies are all very consistent. They all show about one and a half frequency increase in those high fevers.

I'm inclined to in any study try to put safety in the context of efficacy benefit to risk. We always expect with interventions that there are some risks, some safety issues.

Essentially if you're comparing a vaccine against a placebo where the upside is preventing disease, you're going to expect that, or you're going to be willing to accept a higher level of safety concern.

In this setting we're comparing the combination vaccine against separate administrations so it's to my knowledge we're not claiming that it's

being done specifically to improve efficacy, although possibly to improve overall coverage.

But it does make me a bit more concerned about the level of additional safety risks that you all, that you would be willing to accept in a setting where you're not comparing to a placebo but you're comparing to another regimen that is presumably in the same level of efficacy.

The last point is to state maybe the obvious and that is that these data are not addressing the more rare events. It has been noted and it's reassuring at some level to note that there isn't any evidence of anaphylaxis, HHE, SIDS.

But these are events that would to have adequate power take trials anywhere from the size of ten to twenty thousand for us to really be in a position to rule out.

We do see the seven cases of seizures. It's entirely possible that that doesn't reflect a true increase and yet it certainly is possible that these increases in fever would translate to a two or three-fold increase in the risk of something on the order of seizures from a rate of one per thousand to three per thousand and these data obviously aren't of the magnitude that we would be able to address that.

CHAIRMAN DAUM: Thank you very much. Other Committee members, please. Dr. Faggett.

DR. FAGGETT: Yes, I just want to make a point that fever is a pretty good response, physiologically. Let's not forget that. However, in the younger child, there are problems with it. Fevers to the point of hospitalization are a problem.

I still restate my concern about the numbers. Again, it's a vaccine that we are very familiar with the components of, so seven thousand might be adequate. But I think we really need more information and we need to see what happens in more diverse populations as well.

I agree with Dr. Kohl that the preponderance of experience in Germany might not translate or be applicable here. So I have real reservations at this point.

I think that the, I appreciate the full disclosure we've gotten. I think we have the power curve. But I think we really need to really see what this is about.

I wasn't clear on how many of the children had septic work-ups. We implied that. So fever to the point of hospitalization I guess is one of my real concerns.

CHAIRMAN DAUM: Thank you very much. Dr. McInnes?

DR. MCINNES: Do you want me to respond to the number of septic work-ups, or?

CHAIRMAN DAUM: Do you have information about it?

DR. MCINNES: Yes.

CHAIRMAN DAUM: Oh sure. Thank you.

DR. HOWE: So there were only two children in the context of 015 or 011 or 044 so the two pivotal U.S. trials and the 011 study, who underwent a sepsis work-up. And one of the two children, I believe, there was also the possibility that they had influenza. So there was potentially an alternate explanation for the fever.

The other point I wanted to make is that in the hospitalizations with fever and the rates that were quoted in the context of 011, the proportion who were hospitalized with a fever in those who received the Infanrix HepB-IPV was identical to that in the control group.

And I emphasize that this is hospitalization with fever not necessarily for fever. In many cases the children had other things going on which clearly, gastroenteritis, dehydration, an

alternate diagnosis to explain the fever.

So it wasn't, from what we can see, looking very carefully at the data, it's not as if we had a number of cases of unexplained fever, where the children went into for a sepsis work-up, came up empty handed and they said it's related to the vaccine. Does that help clarify?

CHAIRMAN DAUM: It does. Do you want to speak right to this issue?

DR. FLEMING: Right to this point.

CHAIRMAN DAUM: Okay.

DR. FLEMING: Just the distinction that if overall hospitalization rates are much higher than the specific rate of hospitalization for fever.

DR. HOWE: Yes.

DR. FLEMING: Then you could be inducing a five-fold increase in hospitalization for fever and not see an increase in hospitalization with fever if other causes of hospitalization are far more frequent than hospitalization for fever.

DR. HOWE: And the figures that we gave were for hospitalization with fever. Maybe one other thing that might help put this into context is that we did look at the issue of not only how similar were the reporting rates for the common solicited reactions in

the German population as compared to the U.S. population where I think many people have pointed out that for the objective symptoms they were remarkably similar, within decimal points of each other, going from 100 children up to 4,000 children.

In Germany the rate of low-grade fever was identical in those who had received the Infanrix HepB-IPV. But we also looked at things such as serious adverse event reporting and hospitalizations in two studies that we have conducted using Infanrix Hepb-IPV-Hib. One run in the U.S. on a 2, 4, 6 month schedule.

And the other run in parallel, in the same time frame, in Germany and what we found was hospitalization rates and SAE rates, in point of fact they're generally pretty close. I mean usually all of the SAEs are for hospitalization. Were higher in the German population.

So I think it was two point five percent versus one point five percent in the U.S. population. So German children were more likely to be hospitalized. And that's with a shorter follow-up period.

So it's three to five months of age versus two to six months of age. And we consider this to be

indicative of the fact that Germany is a more sensitive, you'll be able to pick up hospitalizations.

DR. FLEMING: And you do not have managed care.

DR. HOWE: Yes.

DR. FLEMING: But the other point too. Do you have a break-out on the age range of the hospitalized comparison, two month, four month?

DR. HOWE: We do have hospitalization by dose which you would be able --

DR. FLEMING: By age.

DR. HOWE: Well by dose will tell you by age. Yes. So let me see if I can get hold of that.

CHAIRMAN DAUM: Okay. In the meantime we'll go to Dr. McInnes and then Dr. Britt.

DR. MCINNES: Dr. Daum, I had a question regarding the ages from the German trial and extrapolating to what the safety profile was found to be in the U.S. And I want to go back to a comment Dr. Howe made earlier today.

I mean I'm impressed with the body of safety data from 011, from Germany. And I'm trying to think about how it's the same and how it's different from the U.S.

I note that the age of presentation for

first dose of vaccine in the Germany study ranged I think between eight and fourteen weeks of age.

I'm trying to think about how a 2, 3, 4 regimen actually when vaccine was really delivered in Germany and how that tied to the 2, 4, 6 regimen in the U.S. And I think you mentioned earlier this morning that, in fact, they looked not that dissimilar.

And I'm wondering if we can go back to the real ages at which the first, second and third doses were delivered in Germany compared with the real ages when the vaccines were delivered in the U.S. Trying to address the comment of how young really were the children at receiving the first dose and the concerns about the work-ups for fever and for sepsis.

CHAIRMAN DAUM: So Dr. Howe, hurry up and produce the first round of data we asked so we bother you for the second. How are you coming?

DR. BALL: Maybe I can make a comment while they're gathering the data. On page forty-seven of the FDA briefing document there are two, three graphs. Dose one, dose two and dose three. And there's a comparison between the groups for study 011 and 015 in the age of the administration.

And you can see that particularly for dose

two there was considerable overlap. There was sort of a biphasic look in I think it was in study 011 in terms of when the administration dose was administered. But you can see that the peaks were different. But there was probably more overlap for dose three.

And then subsequent tables in the, the two subsequent tables, actually I think it's three, compare studies 011 and 015 for each dose and overall for the incidence for both a local reactions as well as general reactions. And I think that it's hard to make sense of these fairly dense tables.

But for fever it was very similar between the two, particularly for a fever of greater than 38 degrees centigrade. For, also for the kinds of symptoms that are more objective. Such as redness and swelling where something was measured.

Those were fairly similar across the two studies. For the events that were perhaps more subjective and maybe more open to interpretation, those were different between the two studies. Such as like loss of appetite and that kind of symptom. So I don't know if that helps answer your question.

CHAIRMAN DAUM: I think it does. And it also has given us an opportunity to let Dr. Howe get

these data up that Dr. McInnes has asked for.

DR. HOWE: Right. So this is the figure from the briefing document, which shows the overlap. The dotted line is the age at vaccination for the first dose, that is from the actual clinical trial 015 in the U.S. and the solid curve would be that for the pentavalent recipients in study 011 in Germany.

And what you can see is that the greatest overlap is dose two. Also, a fair amount of overlap in dose one, dose three, excuse me, some overlap at dose one, but the age of enrollment at age one for study 011 was a bit wider. The eligibility criteria in terms of age at enrollment.

CHAIRMAN DAUM: Thank you very much. Dr. Britt.

DR. BRITT: I just had a quick question about the adverse affects in the fever. Don't know the presenters name, but besides hospitalization, do you have any documentation on antibiotic usage for these children with fever?

DR. HOWE: We do collect information about co-administered medications throughout the course of the trial but we don't have that data analyzed.

CHAIRMAN DAUM: Okay. I'd like to hear from people who haven't addressed this question yet on

the Committee, before I call on them. And then, also other issues that haven't been raised. It's clear that we're collectively, at least everyone who's spoken so far, concerned about the differential rates of fever.

It's also clear, at least from what I'm hearing that people want more information about what the consequences are of those increased rates of fever. And are hearing that we'd like more information about that. So other ideas. Dr. Goldberg, then Ms. Fisher.

DR. GOLDBERG: I just wanted to echo some of the other comments that have been already made. I'm very concerned about the fever as well. Particularly in face of my uncertainty about the efficacy.

I mean I think that to have an increase in a side affect such as fever, we need to be sure that the efficacy really is the same. At least the same.

And I think also that given the size of even the large trial, it is, we really, given that these vaccines are really not that dangerous, it's not surprising that we really don't have very many of them to deal with.

And I think it's unlikely with even the

new trials that we'd be asking, the new trial that we might be asking for with regard to efficacy that we would gather much more organized trial safety data.

And so all I would urge is that at some point we'd be very careful about those surveillance that we put on products such as these to ensure that we are capturing the data, the outcomes and the handling of those severe outcomes so that they can be monitored actively.

CHAIRMAN DAUM: So do you think the data are adequate to address the fever issue and you just don't like the fact that it's there?

DR. GOLDBERG: I don't like the fact that it's there. I don't know who much more could be done in this context.

CHAIRMAN DAUM: Okay. Thank you. Ms. Fisher. Then Dr. Griffin.

MS. LOE FISHER: I'm concerned about limiting the active surveillance for adverse events to four days post vaccination and total adverse event surveillance to only thirty days. And the fact that only 700 U.S. children have been evaluated the 2, 4, 6 month schedule.

And I'm concerned about the seven seizures which occurred in seven thousand children with five of

these being first-time afebrile seizures which are the kind most likely to result in long-term permanent neurological damage.

And I am concerned that without an understanding of the biological mechanism of adverse events, including fever, that when an adverse event occurs, there will be few clues about which component of the vaccine is at fault, or whether it is indeed the combination, thereby leading to confusion about whether to continue vaccinating with the combination vaccine versus eliminating one of the vaccines or giving the vaccines separately.

So I would like to see a larger trial in the U.S. in 2, 4, 6 month-old children, with at least a one-year follow-up to measure for all morbidity or mortality outcomes, including the development of autoimmune and neurological disorders.

This is the first five-in-one vaccine and will have an enormous impact on vaccine policy. And we have to be sure that it's the right one at the right time. Because if it turns out to be far more reactive in a real life setting because we failed to get enough information pre-licensure, then it will ultimately negatively affect the whole vaccination system.

And I think you have to have at least three thousand more U.S. children in your total database so you have ten thousand children that you have studied on this vaccine. So that the public has confidence that you have proven safety and efficacy.

CHAIRMAN DAUM: Thank you. I'm going to try and fill in the cracks here and get comments from people who haven't spoken to this issue so that we can move on. Before I do that though I'm going to call on Dr. Kohl.

DR. KOHL: I've spoken to the issue but I'm wrestling with a question that's sort of a basic question. If, let's assume this vaccine is as effective as the components are. Let's just assume that. And let's assume that the only side affect is increased fever.

And let's take the increased fever that sticks in my mind as a ten percent greater than 101.5 versus a five percent greater than 101.5 in the components.

Would you license this vaccine? Is it worth the extra fever for the convenience and one of the things that I could foresee is physicians finding it so much easier to have this vaccine because they wouldn't have to stock as many different kinds of

vaccines and they'll only give one shot, etcetera.

That not only won't it be licensed but it might be the only one carried by the physician. And one of the questions asked earlier was well would you be able to go to the doctor and still get the other vaccine components if you didn't want this combo vaccine? I could see where lots of parents and their children would not be able to get component vaccine.

CHAIRMAN DAUM: Okay I think we've heard from Dr. Kohl. Dr. Faggett.

DR. FAGGETT: I just want to follow-up with Dr. Kohl's comment. I think a lot of my colleagues in practice in pediatrics would be a little concerned with a couple of four-week, two-month olds with fever, 101, might be enough to discourage them.

I would be concerned of the down side. That we'd lose the confidence of the practicing primary care provider, family practice pediatrician, who indeed is the most effective one in talking to those parents. So I think there is that aspect to it. The fever there would be a real concern.

That they were just getting over the hepatitis B issue and we're now convincing parent that you need to give HepB at birth. So I think that we need to consider that as well. That the pediatrician

has to be convinced that this is a safe vaccine. I don't think that we have the data to do that right now.

CHAIRMAN DAUM: Thank you. Dr. Stephens. We haven't heard a peep out of you on this important issue. Could we ask for a comment?

DR. STEPHENS: Sure. There does appear to be more fever. The data we have suggest that there is more fever. There probably is more local reactogenicity if you look at the data as well with this particular vaccine.

I was kind of surprised by the 027 data because I thought that would be even more impressive. But it wasn't so that's interesting. I don't know quite how to interpret it. In any event, I think that we do see more fever, we do see more local reactions, there may be more seizures. We don't know that.

It's not statistically evident. By certain seven and zero is of concern. So I think there are clearly issues regarding the reactogenicity of this particular product in comparison.

Now from an adult infectious disease perspective, this is, this would be a different issue I think than it is from a pediatric perspective. And I appreciate the comments the pediatricians.

CHAIRMAN DAUM: Thank you. Dr. Faggett, you've spoken. Do you want to embellish your comments.

DR. FAGGETT: Too much.

CHAIRMAN DAUM: Dr. Griffin?

DR. GRIFFIN: Well I think that, I think the big consideration is I think we're all convinced there's more fever and more reactogenicity. And I think the big consideration is what the trade off is there.

And so, you might be willing to have some percentage more children have fever for being able to use only one shot rather than multiple shots.

And even parents might say rather than poking my kid three times, you know, I'd be willing to have some more, deal with fever for twenty-four hours or something like that afterwards. So then I think the real issue becomes what the consequences are of that. And I think that is what we don't really know.

How, you wouldn't be willing to have your child be hospitalized and worked up for a fever because of that, I think, as an additional question. So I think that it really does depend on and in part and that could be seizures or other kinds of adverse events. You know how much it really translates into

significant medical problems to have that increased reactogenicity.

CHAIRMAN DAUM: Thank you very much. Do you think the data are adequate?

DR. GRIFFIN: Adequate for what? I think they adequately say that we have a problem with more reactogenicity. But they aren't adequate to say, I don't think is that in our medical system what the consequence is as far as extra hospitalizations and that sort of thing for these kits.

CHAIRMAN DAUM: Thank you very much. Dr. Diaz. Do you want to comment further? We have heard from you. Okay. Dr. Goldberg, your pleasure.

DR. GOLDBERG: I mean I'm listening, I'm listening to the pediatricians and again it's being on the fence of when is enough, enough. And how serious is the fever problem. And I think that remains unanswered really.

CHAIRMAN DAUM: Mr. Fisher we've heard from you. Do you want to say anything else directly to this question. No. Thank you. Dr. Fleming?

DR. FLEMING: So is it accurate to say we should also be specifically answering the second part as well? If we need additional data.

CHAIRMAN DAUM: Yes. Absolutely.

DR. FLEMING: Okay. I just might begin by just adding to what Dr. Stephens has pointed out that one of your last comments related to the fact that there are the seven seizures versus zero. My understanding of the data I think though is it's pretty tenuous.

If it were seven versus one we would have equal rates. So it's very limited amount of information. I have raised the issue as well stating that it creates the suggestion that this is something to be addressed more reliably as opposed to providing any kind of direct reliable information that there is in fact an increase.

So having said that my sense of the two types of additional information that I would like to see would be tied into what might happen for efficacy. If in fact there is going to be further study to more conclusively address efficacy and immunogenicity related to the earlier discussion today, then I would certainly hope that this would be a great opportunity in the context of that larger comparative trial in the U.S. to more carefully follow, not just what is the relative increase in fever, but the sequelae, very carefully looking at what the consequences appear to be in those instances where particularly higher fever

is occurring.

And in fact I would think that if it involved Prevnar, in the context of Prevnar it would be extremely important to see what that relative rate of fever would be in that context.

The other thing that I would hope for is if that study then is favorable, I think it's not realistic for us to expect as in other settings that we're going to be able to get at the rare event rates.

And so I would, if that study is favorable, and if marketing occurs, then certainly careful follow-up in post-marketing surveillance to get a better clue, particularly about issues such as seizures and sepsis but in general these rare events and is there in fact evidence to suggest that the occurrence of fever is translating into important but rare events that I think probably would have to be reliably addressed in large scale, post-marketing surveillance. So those are the two sources of information that I would hope to get.

CHAIRMAN DAUM: Dr. Broome would you like to go ahead? And then we'll come back to Dr. Wharton in a moment. You had your hand up.

DR. BROOME: Well I particularly wanted to clarify David Steven's comment because I think it's

somewhat important rather than saying seven versus zero, to say seven out of about five thousand versus zero out of 876.

And as Tom clarified, you would expect one at the rate of seven per five thousand. And you'd expect one in the control group. So the fact that you observed zero, I don't think really you know. What it means is what the sponsors and Leslie have told us. The study is not powered to detect rates that occur at the frequency of one per thousand.

DR. STEPHENS: I think the concern is that we see this with the clear increase in fever with the clear increase in reactogenicity. That's my point.

DR. BROOME: I think we all are interested in good probably post-licensure in terms of the frequency of the one per thousand. But I think the issue in terms of voting as I certainly agree with everybody that there is an increase in low level fever and I think this is concerning.

And it's certainly, it would be nice to have additional clarifications on the Febrile episodes and the clinical implications of those Febrile episodes.

I guess I'm a little skeptical that you're likely to get real good quality information on that.

I think the information around hospitalizations and septic work-ups is probably about as good as you're going to get.

So, you know, I'm particularly interested in you know should licensure occur, you know, continued follow-up to focus on both the local Febrile and any other possibly rare adverse events.

CHAIRMAN DAUM: Thank you. Dr. Ball wants to make a clarifying comment.

DR. BALL: Right. This is a clarifying comment. I think Dr. Stephens brought up the issue of the seizure, the difference in seizure between the combination recipients and the control, in the context of the increased fever.

And I think, as was shown in my slides, within the time period in which the fever was observed, the four-day time period, we're not talking seven to zero, we're talking two to zero, in terms of the absolute number of seizures.

CHAIRMAN DAUM: Thank you Dr. Ball. Dr. Wharton? Can we ask you to comment on this issue, question that's on the screen?

DR. WHARTON: Well, I am concerned about the fevers as well. Again I find some reassurance in that they tend to be, they appear to be relatively

low-grade fever with the higher fevers being substantially less frequent.

I think it will be important should the vaccine be licensed to evaluate this in the context of the current recommended childhood immunization schedule.

CHAIRMAN DAUM: Thank you. Dr. Britt?

DR. BRITT: Yes, I'm coming back to just one point. I think, unfortunately, because I do, not unfortunately, that I do interface with community physicians, but I do interface with community physicians in treatment of infants with fevers is not only with antipyretics, it's often with antibiotics, in combination.

So I don't believe that we should ignore this either for a vaccine that may be used for a large number of children which does induce a high percent increase in fever. There may be a concomitant increase in the inappropriate use of antibiotics, which I don't think anyone, I don't think this is hiding needs right now.

CHAIRMAN DAUM: We have three non-voting members at the end of the table but since we're not voting we're about to hear their comments on this question. Would you be willing to give us a terse

view on this question? Dr. Gerber, we'll start with you.

DR. GERBER: Yes. Well, I think as I already said, I am concerned about the increase in fever. As Steve Kohl said, it's a trade off. And no vaccine is a hundred percent safe. And what we need to decide is how much fever are we willing to accept given the potential benefits of this vaccine.

But it's not just how much fever, but what the implications of that fever are going to be. So, it's one thing if it's a temperature of 101 that get's treated with an antipyretic at home, it's another thing if it's going to result in getting antibiotics or hospitalization or physician visit. And I think that's the information that we need.

CHAIRMAN DAUM: Thank you very much. Ms. Libera?

MS. LIBERA: Well I understand that convenience of this vaccine may give you more compliance. I would hope that the convenience or the need, perceptive need, for this convenience wouldn't be the driving force.

CHAIRMAN DAUM: Thank you very much. Dr. McInnes. Not least.

DR. MCINNES: I think I'm sitting where

Michael is in terms of really wrestling and looking at the data that Dr. Ball had prepared on the safety profile following each of the doses from 011 and trying to look at the four pooled groups compared to the group five that received the non-combination Infanrix vaccine and trying to get a sense of how fever, low-grade as well as high-grade fever, sat, per dose, and moving forward.

And I think the picture is, you're left with a sense of this overall increased fever, but I really can't get my hands around what it really means. The categories are broad and I don't really understand the antipyretic use pattern.

It makes me go back and remember ten years ago in wholesale DTP studies where clinical investigators used to send subjects out the door with antipyretic on board already to try to deal with the predictable Febrile response.

And so, I don't really have a handle on, I see the patent, I see the increase in frequency with dose, but I don't really know what it means and whether. I'm not overtly concerned about it but I'd like to be able to look at it more and know more about it.

CHAIRMAN DAUM: So that's your additional

information requested category? Okay. I guess I'll complete this round of comment by saying that I think that data are adequate to make a number of comments about safety. I think that it's clear as many have said that this combination vaccine causes a little bit of excess low-grade and some intermediate-grade fevers.

My sense is that overall the pattern of the vaccine is a safe one. And whether people tolerate the excess of fevers or not, I think is a question to wait for the marketplace to decide. And I would like to see an effort made to gather more data about its implications, but, as a pediatrician, I can guess what some of its implications are.

If we start doing this to millions of children, there probably will be an occasional Febrile seizure. There probably will be an occasional septic work-up. And I think people will have to decide whether they think that's sufficient to not license this vaccine.

I think the safety profile overall that we've seen today is adequate and suggest that this vaccine is safe, but I too am troubled by the rate of fever. And what I would do in my own practice, counseling about saving an injection versus the higher

risk of fever, I think is a, I think is a separate question.

I'm intrigued by one of, comments that only was said once by Dr. Wharton, and that is that the interaction with Prevnar from a point of view of safety. And I hadn't thought of it that way. And it would be pretty easy, I would think, to get enough data to reassure me and a small clinical trial, that looked at them together, to see about whether there's a synergy with fever.

Because that's something I don't think I would be comfortable with. As Dr. Fleming raised a point, I think with the rare events, we have choices here that are almost murderously difficult. One is to do pre-licensure trials so big that we have a confidence down to some minute level of comfort about rate side effects.

And the other is to get trials adequately big so that we as a vaccine community believe that something sufficiently safe to go to post-licensure surveillance and documentation as a way of getting at the very rare events that we hadn't seen any of in the pre-licensure trials.

I'm not wise enough to know the definitive answer to that, but, in general I would come down on

the side of the post-licensure approach being a more efficient one to do that.

So that's a very complicated answer to what might at first seemed like a simple question, but I think we've seen a lot of data about safety and I think that, I hope FDA folks and sponsor folks have heard the concerns and heard the good points as well.

I'd like to move on to the next question now. Could we flash it up on the screen, there. God. Thank you. Discussion Point Three. We've heard a number of comments about this and we might be able to go through this part of the discussion fairly quickly.

And that's, we'd like, the FDA would like to hear us discuss the data submitted in support of the concurrent administration of other routinely recommended childhood immunizations. With this combination, this DTPa-HepB-IPV vaccine. Specifically, they've asked for Hib and Prevnar comment.

So we will again put out the net for general comments or clarifying things we need, but then I'd like to hear some specific comment directed at this discussion. We may have done this one. We may be able to go right to the specific comments. Shall we try? Dr. Fleming would you like to start?

DR. FLEMING: Well the aspect of this that strikes me as being particularly important is the interaction with Prevnar both in terms of effects in immunogenicity and effects on safety. We have been presented some data in our packages that certainly suggest that there could well be an affect on immunogenicity and others on this panel will be much more capable than I to address the fact that there is also the risk of interactions and safety and specifically with fever.

So, certainly I would urge that there be studies, in whichever strategy the sponsor and the FDA wish to pursue for future investigation, very important elements of that should be getting information that will allow us to adequately address overall effects on immunogenicity and on safety, in particular fever, when there's concurrent administration with Prevnar.

CHAIRMAN DAUM: Thank you very much. Dr. Wharton?

DR. WHARTON: On the issue of concomitant administration with Hib, it's nice to see in the material provided in the briefing package, testing of the combination vaccine with multiple different Hib products from different manufacturers. And those data

I find very reassuring in terms of concomitant administration with Hib vaccine.

I am troubled though about the Prevnar issue based on the data provided in the briefing package as well as the more general issue of Prevnar interactions with other DTPa vaccines, as suggested in the Prevnar package insert. And I do think that's an area that requires additional information.

CHAIRMAN DAUM: I point out for no particular reason, except to try and be helpful, is that the company had no opportunity to study Prevnar, because of a variety of things that have occurred since this package was being put together and the approach to the agency and to this Committee was being made.

And so, I think it's perfectly legitimate for the Committee to decide that we need to have this information to reach conclusions, but on the other hand I think we should be careful to not believe anybody should be criticized for the fact that those data aren't here. So I'd like to just off-hand make that comment. And keep going around the circle. Dr. Broome?

DR. BROOME: Well, I mean I would hope that it would be fairly self evident since that's one

of the routine childhood immunizations, we do need to have some data about concomitant administration with Prevnar, particularly in light of the potential for impact on immunogenicity of the pertussis components as well as the question of safety issues.

I think it has been clear that it wasn't possible to include it at the time the initial trials were done. So, I think it's appropriately discussed as the third issue.

CHAIRMAN DAUM: Can I press you about one thing? If it were, if it came down to this, I don't know if it does, but I know input is desired, should, is that information necessary before licensure, or could it be obtained after?

DR. BROOME: Well, it, you know, I would think you would ideally have some before since it is something you're proposing for mass concomitant administration. It's an unfortunate result of timing of availability that that couldn't be done with the initial studies.

But I think the ultimate bottom line is if you've got a product licensed for use in U.S. infants, you'd like to know how it interacts with the currently administered products.

CHAIRMAN DAUM: Thank you. Dr. Britt?

DR. BRITT: I have nothing to add. Those are my sentiments.

CHAIRMAN DAUM: Thank you. Your point of view has already been expressed I presume.

DR. BRITT: Yes.

CHAIRMAN DAUM: Okay. Dr. Gerber.

DR. GERBER: I agree with Linda, I feel very comfortable with the data that were presented on the concomitant use of this vaccine with Hib, both in terms of safety and immunogenicity. As far as Prevnar goes, I think we tell parents that all new vaccines are tested in combination with the current vaccines that they're going to be used.

I think that if we're going to be using this vaccine with Prevnar, which we would, I think that safety and immunogenicity of that combination needs to be established before licensure.

CHAIRMAN DAUM: Thank you. Ms. Libera.

MS. LIBERA: Nothing.

CHAIRMAN DAUM: Okay, Dr. McInnes?

DR. MCINNES: I love the Hib data. I'm very excited to see immunogenicity profile from that. I'm troubled by the concept that this has to work together with Prevnar as a condition of licensure, am inherently troubled by that.

I think in terms of understanding recommendations of how the entire pediatric immunization regimen is going to have to work, we need to see the data. But I'm not comfortable with it being a condition of licensure for this product.

CHAIRMAN DAUM: Post-licensure's okay with you? Thank you. I'm just, I'm not putting words in your mouth, I'm trying to understand what you said. Who's over there. Dr. Kohl. It's you.

DR. KOHL: I'm still over here. I agree with everything my colleagues have said. There's one problem that I foresee. Looking at the Prevnar prescription information it looks like there is already, at least preliminary data, that this Prevnar interferes with some antibody responses of currently-licensed vaccines.

So, I guess what I'm trying to focus, and some of my statistically-oriented colleagues might be able to help me better, is what are we going, how do we set the bar? Does it have to not interfere at all? Or does it not interfere as much as Prevnar interferes with Acel-Imune? How's that bar going to be set? It's an interesting problem.

CHAIRMAN DAUM: And if I could toss in, what about interpreting interference with respect to

pertussis antigens?

DR. KOHL: Right. And is it even fair to. Fair is not the right word, but obviously Prevnar's licensed and all these other preparations are licensed and there may be major interferences there and that's not going to pull those products from the shelves.

But if this one doesn't meet whatever we're going to set it will preclude it from being licensed. So, there's some really sticky issues in the Prevnar and other vaccines.

DR. FLEMING: Should we comment on his, on Steve's statistical question?

CHAIRMAN DAUM: If you could make a brief helpful comment.

DR. FLEMING: Just a very brief comment. It's certainly a very relevant issue as to say, if in fact Prevnar interferes as the evidence that we've seen suggests it does with let's say components of a pertussis vaccine, how do we assess, in a clinical trial, what, in essence, what the impact is now on this combination.

My fundamental principle I guess of clinical trials is that I want to design a study to compare in a real-world setting, benefit-to-risk of an experimental approach versus standard of care. And

so, if standard of care now involves wide-spread use of Prevnar with separately-administered components, then that's my control.

And I want to compare that to the administration with a combination vaccine, presumably in the context of Prevnar there as well. And I want to understand the relative difference. It's possible that if people are accepting the use of Prevnar with single components that diminishes some of the FHA responses, etcetera, that what we will see in that randomized trial is no relative further increase in reduction and that is, in fact, a relevant answer to my perspective.

We would then see that the combination, with Prevnar use, against how the current components are being administered with Prevnar use, doesn't provide any further diminishment of immunogenicity.

CHAIRMAN DAUM: Thank you. Dr. Stephens?

DR. STEPHENS: A couple of comments. One is and we've heard a lot of positive comments about the association with the Hib vaccines. I am troubled though, and maybe Dr. Ball can clarify, on page fifty-four of your hand-out, it is, we've talked, or you've indicated, looks, the equivalencies look very good for this vaccine in combination with most of the Hib

products.

My only concern was on the level, and I mentioned this earlier this morning, on the level of Anti-PRP at one microgram for at least two of the doses, two of the dose schedules. Could you comment on those lower levels with?

DR. BALL: Are you talking about the 2, 3, 4 month schedule, 017?

DR. STEPHENS: Correct. Correct. It's a different schedule, I appreciate that.

DR. BALL: It's a different schedule. I really think that

DR. STEPHENS: It's just a schedule issue.

DR. BALL: I think it may be a schedule issue. Because if you look at

DR. HOWE: It's a phenomena for compressed schedules with Hib. So it's a one, six, ten, fourteen weeks. And the other is 2, 3, 4 months and that explains the results that you see there.

DR. BALL: If you look at the 2, 4, 6, which is at the top for the Anti-PRP response at the one microgram per mL level, it's between eighty-nine and ninety-four percent.

DR. STEPHENS: My concern has to do with the effectiveness of the Hib vaccines as we, if this

were an effect, in terms of lowering levels that might interfere with transmission, and that would be an effect we would not want to see with this vaccine. And so that was the concern I had. And I think you're point is reassuring.

I must say I share the concerns about the Prevnar issues that have been raised by Dr. Wharton and Dr. Broome, in particular, and I think prefer to see this as a pre-licensure issue rather than a post-licensure issue.

CHAIRMAN DAUM: Thank you very much. Dr. Faggett, please.

DR. FAGGETT: Yes. I concur with my colleagues that the Hib data is impressive. And that we need more information about Prevnar. I think really pre-licensure investigation and clarification will enhance exceptions of both, of Prevnar and the combination vaccine.

CHAIRMAN DAUM: Thank you very much. Dr. Griffin.

DR. GRIFFIN: I agree and don't have much else to add.

CHAIRMAN DAUM: Dr. Diaz.

DR. DIAZ: Well, I agree in terms of needing more data, especially on the Prevnar issue.

And I saved one of my safety comments for this round because it's pertinent at this point too.

From a pediatric, pediatrician's standpoint and a parent, I think I would be more than willing to tolerate a little extra fever for having a combination vaccine.

And yet, at the same time, again I think we've raised a lot of issues as to what that extra fever would lead to and sort of where does one draw the bar and I'm sure people have differing opinions of where they might draw the bar but, myself, I wouldn't certainly tolerate a combination along with Prevnar, leading to a higher incidence of fever such that there are many more febrile seizures.

Because when you get off into that realm then you're not only talking about the potential for hospital encounter and perhaps sepsis work-up, but the likelihood that a child will receive a spinal tap. And again, along with that sepsis work-up, is almost a hundred percent at that point in time.

Where somebody might not include the spinal tap if the child was there with just increased fever. Make a clinical judgment and delay that.

So that's where I would draw the bar and I think I would want to know prior to licensure, what

the combination does with Prevnar along those lines in terms of just how much fever and what are the consequences again, as we pointed out, to that fever.

CHAIRMAN DAUM: Pre-licensure? Thank you.

DR. DIAZ: I mean, I hate to say that because I recognize the timing of this and it's unfortunate but better pre-licensure than after, I believe.

CHAIRMAN DAUM: Dr. Goldberg. Not least.

DR. GOLDBERG: I guess I'm concerned about two things. One is I think that the Prevnar issue has to be investigated and ideally pre-licensure. We've also, some of us believe that there ought to be some more combination efficacy trials done pre-licensure.

I have a question, though, to my colleagues. One is the Prevnar issue is kind of unfortunate and almost unfair here. And second of all, is it even possible to study the combination vaccine versus its components without putting it in the context of Prevnar, if Prevnar is being widely used now?

Therefore, I think it has to be incorporated into one new paradigm if you will, for study, unless there's some place in this country you can use, because I'm assuming it's being used and the

kids would be in the trials, but then they would have Prevnar being given outside of the trial.

Which would be far worse that having it incorporated into the trial design and being able to evaluate the total combination and the way it's administered. So I defer to, I mean I'd like an answer actually, from my colleagues about Prevnar use to help me finish my thinking.

CHAIRMAN DAUM: What, you have to form the question a little more precisely, maybe we can get the whole --

DR. GOLDBERG: It's can you today do a trial of this combination vaccine, against its components, without some kind of co-administration or somewhere in the schedule during this period and administration of Prevnar, given, I mean am I understanding this, it's being widely used in these, in children of these ages. I mean?

CHAIRMAN DAUM: Well, it's recommended for, with universal immunization.

DR. GOLDBERG: Pardon?

CHAIRMAN DAUM: It's recommended.

DR. GOLDBERG: Okay. So, therefore, we're in a very sticky situation in requesting a trial of the combination against its components. Without

having be a trial of the combination plus Prevnar against the components plus Prevnar.

So that would be my recommendation in that context and then with one trial we would accomplish pre-licensure what we need.

CHAIRMAN DAUM: Thank you very much. I just end this part of the discussion by saying, with the exception of Prevnar, I think we've been reasonably satisfied that there is unlikely to be vaccine-antigen interference.

The Prevnar issue, with respect to antigen interference, for me, could be done post-licensure. If it interfered with pertussis antibodies, I wouldn't know much about what to do with those data anyway and those are basically my comments.

I do want to say though that I keep coming back to this increased fever issue. And I guess I'm talking a little out of both sides of my mouth, but I would like to see some safety data in a small trial to reassure myself that there's not synergistic fever between Prevnar and this combination.

On that side, I guess I'm siding with the people concerned about safety, Dr. Diaz and others who made that point. So I'd like to move on now to Discussion Point Four. And I think that we've had

enough discussion that we can do this pretty quickly and meet our five o'clock finish.

Please identify any issues that should be addressed in post-licensure studies. Please specifically include a discussion of the safety immunogenicity of concurrent administration of other routinely-administered vaccines, Prevnar. I think we've done that.

Safety and immunogenicity of a fourth and fifth dose of Infanrix DTPa, which we haven't talked about and we need to. Following a primary series of DTPa-HepB-IPV, this combination. And the safety of a primary series of this combination following a birth dose.

So I think the birth dose is one issue we need some discussion on, as is the fourth and fifth dose. And unless somebody objects on the Committee, I think we've addressed the Prevnar issue and the need for studies on that.

Some have spoken to pre-licensure preference and some to post-licensure preference, but discussed, nevertheless, it has been. So, let's deal with the birth dose issue and the fourth and fifth dose issue and any other post-licensure study issues that people want to talk about. Are there general

comments that more information is needed or can we go right to -- yes, Dr. Finn?

DR. FINN: Dr. Daum.

CHAIRMAN DAUM: Yes.

DR. FINN: Just a point of clarification.

CHAIRMAN DAUM: Please.

DR. FINN: I'm not sure if you're reading the question from what's up on the screen versus what's on, in front of you, perhaps.

CHAIRMAN DAUM: Ah. Could be.

DR. FINN: And I would just like to point out that there's an extra clause in there.

CHAIRMAN DAUM: Thank you. You snuck it in.

DR. FINN: Yes. We snuck it in. Apologies. Safety and immunogenicity of the combination following a complete or partial primary series of Infanrix or other DTPa vaccine.

CHAIRMAN DAUM: Oh. Okay. The extra clause is the or other vaccine.

DR. FINN: Right.

CHAIRMAN DAUM: So, it speaks to the booster issue, nevertheless. So --

DR. FINN: To complete the primary, sorry, it's to complete the primary series with the kid who

may have initiated with dose one or two.

CHAIRMAN DAUM: Yes. Thank you. Thank you. Thank you. So we have general discussion on this point and then we will sort of invite point and comment. Or we can go right to point and comment then. Dr. Kohl, start us off here.

DR. KOHL: Let me do what I think is the easier one first. I was satisfied with the birth dose hepatitis B, so I'm not going to ask for anything more of that. I think the, completing the primary series is not something that I would hold for a pre-licensure, but I would like to see that as a post-licensure.

It gets complex because, as we talk about multi-component vaccines, and multi, multi-component vaccines and multiple manufacturer's vaccines, the combinations, permutations get to be a little mind boggling. But I guess we do need that. And, where else are we?

The question of boosters. I think that's not being requested at this point in licensure for a booster. And I think the booster licensure dose should await a further discussion at a different time.

CHAIRMAN DAUM: All right. Dr. Stephens.

DR. STEPHENS: I basically agree with

those comments. I think the hepatitis B data, was at least in my view, convincing enough that I'm not sure that we need in post-licensure kind of study. The other issues I think require further data and post-licensure types of studies.

CHAIRMAN DAUM: Dr. Faggett.

DR. FAGGETT: Yes. I agree with my colleagues' comments. I think we're going to find some variability in terms of the birth dose of hepatitis B, because there's still some concern for some parents, we're getting them back online, but I think its, you're going to find that those parents who don't want that birth dose are probably going to be resistive to the combination vaccine.

So that's going to be a real challenge for us in practice. But I think the post-licensure study of this issue will assist us in better accounts. In the booster issue, I agree it needs to be looked at.

CHAIRMAN DAUM: Thank you very much, Dr. Faggett. Dr. Griffin, please.

DR. GRIFFIN: I agree that hepatitis B I don't think is an issue from the point of view of immunogenicity. I think the only issue is the one I raised before which I just, would be how confusing it starts to get whether a child has actually had the

birth dose or not and what kinds of series they needed and combinations. But I don't this that's an issue for this Committee.

The, and I think all of the other issues can really be post-licensure issues as far as the incredible, increasing complexity of what these different immunization schedules might be as these combination vaccines come on board. And children have had different varieties in different health care situations.

CHAIRMAN DAUM: Thank you. Dr. Diaz.

DR. DIAZ: I don't have anything to add that others haven't already stated, particularly Dr. Kohl, very well stated what I would comment on with the caveat of the birth dose of HepB vaccine. Just to reiterate that this, I feel comfortable with the HepB vaccine, birth dose data that was presented.

Again, only obviously for those children who are born to mothers who are HepB surface antigen-negative. And that would follow along with using the HepB vaccine in a 2, 4, 6 schedule. Again only with those particular children.

CHAIRMAN DAUM: Thank you. Dr. Goldberg?

DR. GOLDBERG: I have nothing to add really. I think the HepB data are adequate and the

other issues should be post-licensure.

CHAIRMAN DAUM: Dr. Wharton?

DR. WHARTON: At least from my understanding from what's in the package, the safety data, the data on the safety of the 2, 4, 6 administration of this product to 2, 4, 6 following a birth dose are limited. That said, this has been an accepted practice in the United States for a number of years and I expect it will continue to be so.

So I think I can probably live with it, but clearly the data that I think have been presented are limited in quantity. Regarding the safety of this. The issue of the indication for use of this vaccine for completing the series, I have no doubt that the vaccine will be used in that way once it is licensed. I think doing those studies is bound to be difficult.

And clearly if information is needed on that it should be obtained post-licensure as that will be how the vaccine will be used to complete the series in those children who have already started the series with the individual vaccines. And I don't have concerns with that practice. I believe it is likely to be safe and effective but monitoring that in the post-licensure setting would seem to me to be

appropriate.

CHAIRMAN DAUM: Thank you. Dr. Broome.

DR. BROOME: I think the thing we haven't commented on much is data that I assume will be forthcoming which is the impact of the booster doses. But I think it will be real important to take a careful look at those.

CHAIRMAN DAUM: Yes. I agree with you totally. I think that that's a separate whole concern for this Committee for the agency or sponsor, whatever the right -- of consideration ought to be but I don't think that's an add-on consideration or a given that it's either safe or effective. And I think we should really study that very carefully. Dr. Britt?

DR. BRITT: I have nothing to add.

CHAIRMAN DAUM: Dr. Gerber?

DR. GERBER: I have nothing to add.

CHAIRMAN DAUM: Well. I have nothing to add except for what I just said embellishing or agreeing with Dr. Broome's comments. And I think that brings the Committee's business to a close for the day, barring Dr. Midthun's appearance at the table.

DR. MIDTHUN: This will be short. I wanted to come back and I'm looking at Dr. Fleming because he had addressed this and I'd like a little

bit more discussion on this. The question had been raised with regard to Prevnar.

And the potential for interference with some of the pertussis antigens and I think that you had indicated that what you would envision as a control arm for such a study would sort of be what is being done right now. I just want to make sure I understood that correctly.

In other words you would take the routinely-recommended vaccines, they're being administered right now. Let's say for example, Infanrix, Hepatitis B, Hib, and Prevnar and I'm missing one, IPV. And so that would be the control because that's what's currently in practice.

And then the study arm would be the combination vaccine plus Prevnar, plus Hib? Do I understand that correctly.

DR. FLEMING: Precisely. What I would assume is that standard of care, as it's currently being delivered, has factored in the benefits that are understood from each of these vaccines. And the theoretical or real risks that might be incurred, based on the effects that a given vaccine, like Prevnar may have on other vaccines, such as pertussis vaccines.

And in that setting I could readily believe that the benefit-to-risk is favorable because you're targeting a specific disease and influencing the occurrence of that disease and that is a benefit that offsets the theoretical, possibly negligible, possibly meaningful, risk to another disease, in this case for example, pertussis.

So, I will assume that standard of care has evolved in a way that judgment has led to a weighing of the known benefits against the known risks or perceived risks. What I want to know then is, if I change standard of care, in this specific case, by altering the administration of several of these vaccines in a combination form, what influence will that have overall on the safety profile and on efficacy, or if I can't get efficacy directly, on appropriate measures of immunogenicity?

So I would think that the very trial that would be the most natural one to do, would give me very important, real world answers. It may well be that, this is something that requires more than a quick response, that that study design might have some kind of stratification in it so that you ensure a proper balance, because there is a heterogeneity in what that standard of care administration would be.

CHAIRMAN DAUM: Thank you. Now that we've reopened the conversation. Dr. Kohl.

DR. KOHL: What if Prevnar really decreases the efficacy of pertussis vaccines?

CHAIRMAN DAUM: Do you mean efficacy?

DR. KOHL: I mean efficacy. Clinical efficacy or pertussis. It looks like it may decrease the antibody response, in a preliminary look at the Prevnar package insert. What if it really decreases efficacy?

And I can't envision a place where we can do an efficacy study. What I'd be interested to know is if my statistical colleagues can design a thought experiment where they can run kind of sensitivity data to show that if it reduces the efficacy to such and such a point, then the increased lives saved by the Prevnar is actually, is more than offset by the increased deaths or morbidity or whatever from pertussis.

DR. FLEMING: Should I respond?

CHAIRMAN DAUM: Sure. We're in outer space now.

DR. FLEMING: This is a good point, Steve. And it's one that I would say is particularly relevant to Prevnar and discussion about it's use, more so,

than specifically the discussion today about the combination vaccine question. What you've said is a very important issue. And it needs post-marketing study as it relates to the continued use of Prevnar.

CHAIRMAN DAUM: And I would have a plea that the post-marketing study be designed if it's going to look at immunogenicity, alterations in pertussis antibodies to something that we know is biologically and clinically relevant to decreased efficacy.

Because I think we spend a lot of time worrying about a ten percent or five percent decrease in one or another pertussis antibodies. Without having any idea of what the consequences are for effectiveness. Dr. Broome?

DR. BROOME: Well, on the day we reach a hundred percent coverage of Prevnar, we're going to be in trouble. But in the meantime, that's why we do surveillance for vaccine-preventable diseases and do follow-up studies to assess whether there's any, like a case control approach suggestion of increased effectiveness.

CHAIRMAN DAUM: Thank you for reminding us of that. Last comments. We're ready for an on-time arrival here. It's five o'clock, or four minutes to

five.

Nancy has asked me to give special thanks to those who braved the weather, those who are under the weather, and those who weathered red-eyes to get here. And thank everybody who presented and had a stimulating conversation here today. Tomorrow morning at eight a.m

(Whereupon, the above-entitled matter was concluded at 4:58 p.m.)

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: March 7, 2001

Place: Bethesda, MD

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