preventive vaccine.

Approval of most drugs and other therapeutic products are based on substantial evidence of efficacy from at least two well controlled clinical studies.

Substantial evidence for drugs and therapeutic products is commonly determined by hypothesis testing using an acceptable level of statistical significance, usually less than .05.

For preventive vaccines, much more emphasis is placed on the efficacy estimates and the 95 percent confidence limits. For most preventive vaccines, efficacy estimates are relatively high, and confidence intervals are substantially above zero.

Well, decisions about the approval of Prevnar for prevention of acute otitis media could have implications for the approval of other pneumococcal vaccines. Current thinking at the Office of Vaccines is that an indication for prevention of otitis media should stand on its own because license applications for other new pneumococcal vaccines for prevention of acute otitis media may not include evidence for prevention of invasive disease.

Approval of an otitis media indication for Prevnar would set a precedent for the level of efficacy, the type of data, and the preferred endpoints for licensure of other pneumococcal vaccines whether or not license applications for

these other products include evidence of efficacy for prevention of invasive disease.

One possible scenario that Dr. Siber also discussed this morning is that it's possible that a different vaccine could prevent more acute otitis media episodes, but still have less vaccine serotype specific efficacy. That's a possible scenario.

Well, if evidence of efficacy in preventing acute otitis media is judged adequate, then a new indication that describes the treatment effect of Prevnar regarding acute otitis media will be included in the label indication.

The sponsor proposes an indication for prevention of AOM limited to serotypes represented in Prevnar. Some considerations here include that that indication would reflect the primary endpoint in the Finnish study, but not the primary endpoint in the Kaiser study.

Also, focusing on serotype specific efficacy does not capture the treatment effect for vaccine related serotypes, nor the negative efficacy for unrelated pneumococcal serotypes.

Efficacy estimates were relatively low for some of the outcomes and confidence intervals were relatively wide for some of the outcomes.

Well, in the risk-benefit assessment of product approvals by FDA, substantial evidence of clinical benefit must be provided from well controlled studies. A decrease in office

visits for otitis media and potential cost savings of medical care related to otitis media have been cited by the sponsor and in the literature among the benefits of Prevnar related to otitis media.

To the extent that office visits reflect patient disease, they may be considered in the assessment of clinical benefit for the basis of a regulatory decision. However, economic benefit is not considered in the efficacy evaluation by FDA.

Approval of an indication for prevention of otitis media would normally allow the manufacturer to distribute marketing materials promoting use of the product based on information included in the approved labeling. Concerns have been expressed about unrealistic public expectations regarding the effect of Prevnar and acute otitis media.

The potential for misleading public expectations with marketing materials exists for all products and all approved indications. However, FDA is empowered to restrict unrealistic marketing claims. Regulations require that advertisements and promotional labeling be submitted to Siber for review, and any advertisements that are judged false, lacking in fair balance can result in a product being misbranded and then multiple corrective actions are then possible.

That concludes my presentation.

CHAIRMAN DAUM: Are you going to have a

statistical presentation also about --

DR. PRATT: There won't be a separate statistical presentation. However, we're happy to take questions relating to the statistics.

CHAIRMAN DAUM: Okay. Then I think the way we'll proceed is that we'll open the floor. We'll thank you, Dr. Pratt. Then we'll open the floor to the committee for questions and comments on your presentation with respect to clarifying what was said.

Ms. Fisher.

MS. FISHER: That was an excellent presentation that we can always expect from you.

I have a question. What is your definition of substantial evidence of clinical benefit? Does that mean clinical benefit to the individual child?

DR. PRATT: I think we mean by clinical benefit to the individual. What is substantial, I think, is open to interpretation, and we'd be interested in hearing the committee's views on that as well.

As I said, for drugs substantial evidence usually means two well controlled studies and statistical significance at the .05 level.

CHAIRMAN DAUM: Dr. Glode.

DR. GLODE: I'm referring to page 22 of your handout. It's about the PE tube placement issue.

DR. PRATT: Right.

DR. GLODE: And this is my question. In the Kaiser study there was a statistically significant overall reduction in all episodes of otitis media. That was not found in Finland, but the study was not powered to show that effect.

DR. PRATT: That's correct. The estimates were actually quite similar.

DR. GLODE: Right. Okay. If we now go to PE tube placement, and so my question has to do with the power of the study to show an effect in Finland. So there is a reduction. It looks to me like approximately 13 percent.

The prevalence or incidence of PE tube placement was higher; I understand that, during the early period than usually occurs in Finland, but was the study powered to show if there had been a 20 percent reduction, would that have been statistically significant?

DR. PRATT: Right. The Finnish otitis media study actually did not look at tympanostomy tube placement as an endpoint. That was something that the FDA requested during the review period, that they go back and look at that. We were looking at consistency of effect with what was observed in the Kaiser study.

So, no, the study was not planned to look at that at all.

DR. GLODE: And then could I ask one quick follow-

up?

So, I mean, was your conclusion that it was consistent or inconsistent? In the Kaiser study it showed a significant reduction, and in the Finnish study it didn't. Isn't the early period more comparable between the two studies as opposed to that late follow-up?

DR. PRATT: That's correct. I think that the early period is much more comparable.

Yes, they were not consistent. Again, you know, with the reservation that this study was not really designed to look at that, I think maybe the ascertainment of all of those tympanostomy tube placements might be in question, though they actually found that the rate was quite high. So I guess ascertainment was fairly good.

And, yes, the ascertainment or the number of ear tube's placement was higher than expected, I think, in that study.

CHAIRMAN DAUM: Thank you.

Dr. Markovitz.

DR. MARKOVITZ: Yes. I'm curious. Is there any precedence from the FDA point of view for this committee being asked to approve an indication with such low sort of levels of efficacy? Has this come up before just for historical purposes in helping us think about this?

DR. PRATT: I think for an historical perspective

I might turn to Karen Goldenthal or Karen Midthun.

DR. GOLDENTHAL: We have considered some vaccines with lowish efficacy or lower than usual, if you will. One example that comes to mind was a typhoid vaccine, Typh Vi, and as I recall the point estimate of efficacy was about 55 percent and 74 percent for two trials, respectively.

And, of course, that vaccine was approved. I also think that there's some older vaccines that might have lower, you know, efficacy.

Dixie, it looked like you were --

CHAIRMAN DAUM: Thank you, Dr. Goldenthal.

Dr. Snider is next.

DR. SNIDER: Yes, i was just going to mention from my old days BCG vaccine efficacy, of course, would be one where you would be looking at lower efficacy.

Also, there is the issue that we have to confront here around semantics because if you really start looking carefully at the words that you're using, it's sort of analogous to saying, let's say, for BCG vaccine, for example, how much pneumonia do you prevent or with measles vaccine, how much skin rash do you prevent.

Because acute otitis media is due to multiple different organisms, probably mostly viruses. So when you start looking at more ill defined endpoints, then obviously efficacy goes down, and it would go down for other vaccines that we've

licensed as well if you use endpoints that are less specific.

So I just wanted to raise that issue because I think we are confronted with the semantic problem as well as the scientific issue.

CHAIRMAN DAUM: Thank you, Dr. Snider.

I'd like to pose a question before I call on Dr. Katz, and it goes to the question that was asked before about precedent perhaps. Here we have a licensed vaccine with some rather stunning efficacy performance data against invasive disease, and now the very nice data that Steve showed us this morning in terms of what happened since it's been out there.

We have at least two committees that I'm aware of, and probably more, that have recommended this vaccine be given to every child born in this country, and that is if we can keep the supply chain going. That, in fact, is happening and will continue to happen.

So I'm not quite clear how the agency, and I'd also like to hear how the sponsor views this request for an additional indication. I'm not clear exactly what it means. We're already using the vaccine in a licensed way with a very acceptable safety profile and a wonderful efficacy trial for everyone. What will change if acute otitis media is added to the package insert?

I'd actually like to hear from both the agency and the sponsor in terms of the implications of what we're talking

about here.

DR. PRATT: Well, I think anything that goes into the vaccine label can serve as the basis of promotion.

CHAIRMAN DAUM: Promotion meaning advertisement?

DR. PRATT: Advertisement, yes.

CHAIRMAN DAUM: So that's how the agency interprets this request.

DR. PRATT: Well, I think it's one interpretation.

Karen, do you have something to say?

DR. GOLDENTHAL: I also think that the agency believes, as Doug mentioned in his presentation, that the indication would have to stand on its own merits.

CHAIRMAN DAUM: Would the sponsor care to comment on this before we move on to Dr. Katz, then Dr. Overturf?

DR. SIBER: All right. Let me talk about two aspects of this. From a purely scientific and communications point of view, I think having a package insert that describes the effects of a vaccine that are published now and widely discussed and does so in an accurate way that is carefully reviewed between the sponsor and FDA is in the interest of proper communication about the benefits of the vaccine and its effects.

In the absence of that, physicians and parents are left to draw their own conclusions from media reports or whatever sources they might have, and I don't think that may be as accurate as what would be written in the body of the insert.

Another issue about which I am not the best person to comment is that there are, I understand, constraints on what our staff are allowed to say when there is no mention of an indication in the package insert, which is not in the best interest of accurate communication when you're constrained in that way.

From the vantage of whether it's an indication or not, I think the issue becomes the one at least from my scientific vantage, the one I mentioned, and that is if the standard for licensing a vaccine is some benchmark of efficacy against a syndrome caused by many agents, it would put a real chill on the potential.

Let me give you an example. A non-typeable Hemophilus Moraxella vaccine, which a number of manufacturers are working on, I don't think will have much more of an impact on otitis media than a pneumococcal vaccine. It will probably cause a similar number of otitis medias.

And one would want ultimately a vaccine that covers those pathogens. I don't see a way to license that vaccine. If you all tell us that while ten percent effect or eight percent effect or whatever, it's just not going to cut it as an indication.

The only indication for that vaccine perhaps in children would be otitis media.

CHAIRMAN DAUM: Thank you very much, Dr. Siber,

Dr. Pratt.

Dr. Katz and then Dr. Overturf, and Dr. Stephens.

DR. KATZ: I had a comment which maybe has passed by, which was about the efficacy of vaccines and licensure. This is a very major argument, as many people around the table know, when you talk about HIV vaccines.

How much will you invest in vaccine research, development, and licensure of a vaccine to prevent a disease that's 100 percent fatal, but this vaccine may only protect 30 percent of people or it may only prevent clinical disease, but viremia will continue?

There are a lot of these issues that are certainly going to be faced when HIV vaccines come to licensure, but it's apples and oranges, I realize.

I wanted to ask a question maybe of Richard Schwartz. Frequently the statement is made that of all otitis media that occurs, pneumococcal is more aggressive, more virulent, apt to be more overt. So that the question of percentage may also be modified somewhat by that.

Can you corroborate that or deny it?

DR. SCHWARTZ: Based on both experience over a long time, oh, 25 years maybe, and published research that Dr. Rodriguez and I did where we looked at this was culture proven acute otitis media, looking at different pathogens that were obtained from the middle ear fluid, and comparing that with what

the appearance of the eardrum and the height of the fever were at the time of presentation, those who had streptococcus pneumonia or pneumococcus had higher fevers, statistically higher fevers, and also a more angry appearance, more red, if you will, but more than red.

The drug, it's not just a red eardrum that's bulging. It has a very thinned out appearance. Often the epithelial cells on the surface of the eardrum that you're looking at begin to peel off. So there's a very noxious organism inside that's causing this drum to undergo some anatomical changes. It's dying. It doesn't die completely, but at least the outer layer peels off just similar to a bad sunburn. In fact, it looks like a bad peeling sunburn.

So somehow pneumococcus is meaner. It's not only meaner by look. Of the three major organisms, it's the only one that has any substantial bearing on separative complications of ear infections, such as acute mastoiditis.

If you look at pneumococcus, Haemophilus influenza and Moraxella, only the pneumococcus is incriminated of those three in acute mastoiditis, sa well as Group A strep. and sometimes staph.

But the other two, pretty much they're middle ear bugs, and they stay in the middle ear, assuming we're talking about middle ear infections. They don't go anyplace. They usually don't do very mischievous things, and they don't have the

same import that the pneumococcus does.

CHAIRMAN DAUM: Thank you.

I'm going to try and return the committee to the issue of the FDA presentation primarily and ask Dr. Overturf and Stephens, who are waiting patiently, to direct questions to Dr. Pratt and clarify anything that they wish him to comment on.

Dr. Overturf.

DR. OVERTURF: I'd just like to reiterate again two major agencies have recommended that all children less than two years of age in schedules that were in the original application and were approved. And actually most of this additional data really is embodied in children less than two years of age, for which we already have an indication.

So the issue really is -- one is to put in new language that would include otitis media. The other issue is: is there a different process for including data on otitis media and the outcomes of the vaccine on otitis media without putting an indication in the package labeling?

Does the FDA handle that differently at all?

Dr. Pratt mentioned that we can amend safety data. The issue is: can you amend data or can it be put in the application without a specific recommendation for an indication?

DR. PRATT: Right. Data can be included in the clinical pharmacology section of the label without an indication. That is a possible way to include data.

DR. OVERTURF: But that's not one of the questions you're asking.

DR. PRATT: I see Dr. Midthun wants to comment here.

DR. MIDTHUN: I guess I'd like to speak to that. I think in general -- can you hear me?

Okay. I think that in general we do not like to include data in the clinical study section of the label if we don't believe that those data actually -- especially for efficacy data, if we don't feel that the data really support the efficacy of the particular outcome that's being described.

CHAIRMAN DAUM: Thank you for clarifying, Dr. Midthun.

Dr. Stephens and then Dr. Snider, please.

DR. STEPHENS: I'd like you to comment on two questions that were raised in your briefing. One is this issue that I think was also raised in the New England Journal of Medicine about the less credibility. If we approve this as a recommendation, will this have less credible effect upon the current recommendations, given some of the issues in terms of percentages and so forth of efficacy? That's one question.

And a second has to do with the standards for the licensure of other conjugate pneumococcal vaccines and whether in your mind this will enhance, decrease, change those standards.

DR. PRATT: I think what respect to the first

point, the comment in the New England Journal. I really don't have any comment on that. That is a comment from one of the correspondents. I have no comment on that.

With respect to whether this would make it easier or more difficult for a pneumococcal vaccine to be licensed, it's hard to say. As I said in my presentation, I think it would set a precedent for the type of data, the endpoints that would be of interest, and the level of efficacy.

They did provide two well controlled clinical trials. Each one of them met the primary endpoint. I think that would set a level of efficacy for this indication.

CHAIRMAN DAUM: Thank you very much.

Dr. Snider, please, and then Dr. Decker.

DR. SNIDER: I had two issues. One, I would wonder if FDA or the sponsor had any further comments about efficacy against serotype 19F, why there may be less efficacy against that particular serotype in this vaccine.

I noticed, but it's just a subjective impression, that it appeared to me there was less boosting of the serological response on a percentage basis from the third or after the fourth dose with 19F, even though the GMCs were in the range.

So I'd like some comment on that.

Also, I'd be interested in some additional comments about this business about replacement and whether there is replacement with other serotypes and how you view that, if

there is replacement.

I'm confused because Northern California Kaiser didn't seem to see replacement in a more general way, I guess, but whether that means replacement with serotypes that cause less severe disease and whether those are serotypes that are also less likely to be drug resistant, and whether those, also, that are less likely to be drug resistant are just less common in the population and, therefore, been less exposed to drugs.

I guess I don't understand the biology here of why some serotypes are more drug resistant than others.

DR. PRATT: Maybe taking the second point first,what was the second point again? I'm sorry.

(Laughter.)

DR. SNIDER: Is there really replacement, and if so, what is the significance of that?

DR. PRATT: Right. Well, I think the antibiotic resistance is clearly most common in those serotypes included in the vaccine. Replacement was observed in the context of the Finnish study. It's not clear whether that will actually occur in the general population. Again, this was from ear tube taps.

There may also be some data about nasopharyngeal carriage and whether there might be replacement there. I think I've seen some data to that effect from Ron Dagan.

But for the time being anyway, to the extent that vaccine serotypes are replaced by non-vaccine serotypes, it

appears that one would be replacing more resistant organisms with more susceptible organisms.

Over time there may be antibiotic pressure on these as well, and they could also become resistant over time.

CHAIRMAN DAUM: ?Dixie, does that address your questions or are we leaving one out?

DR. SNIDER: Nineteen F.

DR. PRATT: Nineteen F. We also observed what you saw, that the booster responses were not quite as robust as some of the other serotypes, but I don't have any real insight into the differential efficacy for 19F. The sponsor may have some insight.

DR. SNIDER: What would be the efficacy if you took out 19F? I mean, would it jump up substantially?

DR. PRATT: We didn't analyze it that way. So I can't answer that.

CHAIRMAN DAUM: Let's move on to Dr. Decker, then Dr. Parsonnet.

DR. DECKER: Dr. Midthun mentioned that FDA feels that evidence of efficacy robust enough to be in the clinical pharmacology section -- let me rephrase that -- that evidence of efficacy should not be in the clinical epidemiology section unless it's robust enough to support an indication.

Did I paraphrase that correctly?

DR. MIDTHUN: Yes.

DR. DECKER: Does it then hold by inference that evidence of efficacy robust enough to be long in the clinical pharmacology section should be supporting an indication that should be added?

DR. MIDTHUN: It would depend on how the study was conducted and what the primary endpoint of the study was and what had prospectively been planned to be demonstrated. So I think there would be a number of different factors that one would have to consider.

DR. DECKER: But assuming those were met, if it's good enough for the clinical pharmacology, it's good enough for an indication?

DR. MIDTHUN: If the sponsor were to request this indication and the data supported it, and it had been prospectively indicated as being a major outcome in the study, you know, yes, in general that would be the case.

CHAIRMAN DAUM: Thank you.

Dr. Parsonnet, please.

DR. PARSONNET: It seems to me that one of the obstacles that we're hitting is just this semantic one of having this specific indication listed, this one specific one. And it seems to me just by looking at the proposed indication that when you talk about invasive disease and otitis media, you're basically covering 99.9 percent of all diseases caused by pneumococcus in children.

So I'm wondering if it's within our domain to suggest potentially having a different proposed indication which might be for active immunization of infants and toddlers against disease caused by Streptococcus pneumoniae due to the capsular serotypes; get rid of any specific indication; and then leave that in the text to talk specifically about the data for each of these indications.

CHAIRMAN DAUM: My understanding -- FDA people, feel free to modify -- is that we can make comments about most anything we like, but --

(Laughter.)

CHAIRMAN DAUM: -- but the business at hand is to address what's requested, and to decide how we feel about that, and so that everything you say is recorded. People are paid by various companies and groups to pour over your comments, and please feel free to make them because they will be noted.

On the other hand, we can't directly rewrite what's requested today.

Dr. Katz and then Dr. Schwartz.

DR. KATZ: Again, it may be a little bit apples and oranges, but when you license measles vaccine and you say it prevents measles, you don't say on the front line it prevents measles encephalitis or it prevents subacute sclerosing pan encephalitis.

When you read the small print and you read the

papers, you say, "Okay. Measles encephalitis occurs one in 700 or one in 1,000 cases. Maybe after vaccine it occurs one in 100,000 cases."

Measles causing SSPE occurs one in 100,000 individuals. Maybe after vaccine it occurs one in a million or more, but there is nothing in the front line statement that says measles vaccine protects against measles encephalitis or SSPE.

That was comment one. Question two, and this may go down alone with Julie's in a different way. I don't know if either the agency or the producer would consider a modification of the statement. Instead of active immunization of infants and toddlers against invasive disease and otitis media, say against invasive disease and to a lesser extent otitis media.

CHAIRMAN DAUM: Thank you, Dr. Katz.

Dr. Schwartz, please.

DR. SCHWARTZ: I may have a unique position in being in front line practice compared with almost everybody else who's academician, and one of the concerns, potential concerns, that I have because it's already happened is that the pharmaceutical representatives for the company use the stated prevention of acute otitis media as a reason for using one of the antibiotics that the same company manufactures, which is Sufixene (phonetic), saying that since we've already done away with the worry about pneumococcal acute otitis media because of the vaccine, you don't have to worry about using amoxicillin

clavulanate or anything. You could just go to Sufixene and hit bacteria number two and three, which is Haemophilus influenza and Moraxella catarrhalis.

And I have a concern that this may intensify with approval for this indication. I don't have a problem with the data. I have a problem with what it means.

CHAIRMAN DAUM: I think at this point we've probably exhausted our need to quiz and query Dr. Pratt, and I'm going to thank him very much for a fine presentation also, as we thank the sponsors for a fine presentation as well.

What I'd like to propose that we do now is to break and go to lunch. It's two minutes to 12. We will resume promptly at one o'clock right here.

Thank you very much.

(Whereupon, at 11:58 a.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m., the same day.)

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

(1:03 p.m.)

CHAIRMAN DAUM: While we are settling down, I'll tell you FDA has asked us to reflect on based on this morning's presentations. I'm going to ask Dr. Pratt to please read the questions to us so we can focus, and then Dr. Midthun was going to make a comment briefly, and then we will have general discussion among the committee on issues that you feel need to be addressed in your minds before we vote and address the questions directly.

So Dr. Pratt first.

DR. PRATT: Okay. The first question is a two-part question. Are the data adequate to support efficacy of Prevnar in infants and toddlers for prevention of otitis media caused by Streptococcus pneumoniae due to capsular serotypes included int he vaccine?

If not, would additional analyses derived from the Finnish otitis media study, the Northern California Kaiser Permanente efficacy study, or additional clinical trials be useful in establishing efficacy?

The second question: please discuss the strength of the data with respect to secondary otitis media outcomes.

(a) Acute otitis media episodes cause by Streptococcus pneumoniae regardless of serotype;

(b) Overall reduction in acute otitis media

episodes;

(c) Frequent or recurrent otitis media; and

(d) Tympanostomy tube placement.

CHAIRMAN DAUM: Always easy questions.

Dr. Midthun, an orienting comment for us, please.

DR. MIDTHUN: I just wanted to state that what we're really interested in is the committee's opinion on whether the data support the efficacy for prevention of serotype pneumococci in the vaccine. Obviously the discussion will be, you know, very helpful to us, and we'll certainly use it as we, you know, consider this application further.

But what we're really looking for is your input on whether you believe that the data are adequate to support the efficacy.

Thank you.

CHAIRMAN DAUM: Thank you.

I think what I'd like to do is allow sort of dealer's choice now. So committee members can feel free to ask clarifying questions or raise issues that they think should be discussed, and we're not going to vote or directly address the questions quite yet until we sort of run out of things to talk about a little while.

Maybe we're further along than I thought we were.

Dr. Decker.

DR. DECKER: All right. I was going to wait for

some questions, but I don't see any. So I'll lead off.

This is very interesting because as you pointed out, Bob, and as we all know, basically apart from our limitations of doing what we want to do, every kid in the United States gets this vaccine already, and so from that point of view you could argue that this is largely irrelevant.

But it's not. It's actually a very important question. As was pointed out by both FDA and the sponsor earlier, this is one of our first forays into that complex area where we have to look at a multi-factorial disease for which we have what appears to be solid evidence of excellent control for one of the factors and decide whether that's good enough to grant an indication to that particular vaccine for that, recognizing that it covers no more than at best a slim majority, perhaps depending upon your viewpoint a small minority of the cause of agents of the disease in question, particularly in light of the fact that if everybody already gets the vaccine, it would be easier to take a conservative stance and say, "Well, let's not stick our nose into that. Let's just let things be as they are. Everybody is getting it anyway."

But the consequence of that would be severe. There would be a number of vaccine programs that would be terminated, development programs that would be terminated if the committee did that because a lot of the problems for which solutions are being sought over the next decade or two are

problems like this for which sponsors will come in with vaccines proven and well controlled trials to be efficacy for the specific issue, but which clearly in the larger context of the disease are only partial solutions.

If you turn down every partial solution, you never have a complete solution. So that's the problem that faces us.

I note with interest that the FDA clarified in their presentation that the proper consideration for licensure, or in this case for adding the indication to the license, is substantial evidence of clinical benefit, must be provided from adequate or well controlled studies.

And I note with particular interest that that does not say evidence of substantial clinical benefit. The clinical benefit is not for this committee to measure. It is the evidence that is for this committee to measure.

As a practicing physician what I expect of the FDA is that they will insure that the pharmaceuticals available to me have been proven safe and effective for their labeled claims.

Whether or not they're a wise public choice or a wise individual choice for the particular patient in my office at that moment isn't for the FDA to say. Other groups or I myself answer those questions.

I think what we've seen from the evidence presented today is that we've got solid evidence of clear-cut efficacy and safety for the requested label indication. So to

me, this is a very simple meeting, and the answer clearly is to approve it for those indications.

CHAIRMAN DAUM: Thank you, Michael.

Your comments raise a question which I might ask Dr. Pratt, Goldenthal, and others to comment on with respect to Question 1. The question is worded to ask if the data are adequate to support efficacy.

So do you want us to reflect on whether we think the data demonstrate efficacy, in which case it may be a simple question, or do you want us to for further and talk about whether we think there should be an indication approval?

DR. MIDTHUN: We want to know whether you believe that the data support efficacy. We don't traditionally ask the Advisory Committee to actually vote on approving or not approving something, but certainly you're welcome to comment in any way.

CHAIRMAN DAUM: Okay. We continue to seek clarity. Other committee members, comments?

Dr. Glode.

DR. GLODE: I stuck on the issue of whether the condition which is going to be prevented -- whether the seriousness of that condition should have any bearing on the degree of efficacy. So there is statistically significant efficacy, and so I struggle with if this were, in fact, a presentation about a conjugate pneumococcal vaccine for prevention of invasive disease, and it's better than the control

vaccine and reduces invasive disease by seven percent, would I consider that to be of clinical benefit?

And so should I have a different judgment because I'm dealing with otitis media instead of invasive disease? That's my issue.

CHAIRMAN DAUM: Does anyone want to answer that?

Go ahead.

DR. DECKER: I was just sort of going to comment on that because I think that the issue is -- I mean severity may be one of the issues, but I think the other issue is that we're really talking about a syndromic process here, and we're talking about even for the invasive disease indication that was to prevent invasive disease by these serotypes.

And so here we have the same thing, preventing otitis media by the serotypes, and personally, I think the data is very strong in two well controlled clinical trials that it does do that, but what gets people hung up is that it makes a relatively small impact on overall acute otitis media.

But as Sam pointed out and Dixie pointed out earlier, if it were measles vaccine for preventing rashes rather than measles vaccine to prevent measles, you know, then they would have a smaller impact on overall rash disease or overall pneumonia if you're talking about something else.

So to me it helps a lot just to focus down on the actual causes of the otitis media, and the FDA or other people

are going to have to deal with this bigger issue of how it's marketed relative to the overall problem of otitis media.

CHAIRMAN DAUM: Thank you, Dr. Griffin.

Dr. Snider and then Dr. Whitley.

DR. SNIDER: I'd like to basically agree with what Diane just said and just emphasize what a bad precedent I think it would set to use the paradigm of a seven percent reduction of acute otitis media because it would really say that ten in the future you have to look at other vaccines according to the same kind of syndrome.

So you would have to look at pneumonia reductions. You'd have to look at rash reductions, that that would be a totally different paradigm that we've used.

And so I'm very supportive of using the clear endpoints related to these specific serotypes of Streptococcus pneumoniae.

Having said that, I have some questions about whether, again, going back to my favorite serotype here, 19F, and whether efficacy really has been demonstrated for that particular serotype adequately from the trials done thus far.

Now, you can argue that in the aggregate, you've shown efficacy for all of the vaccine, all of the serotypes included in the seven-valent vaccine, but have you shown it for 19F?

DR. GRIFFIN: And the only data that's relevant to

that really is the Finnish data, right?

DR. SNIDER: Right.

DR. GRIFFIN: Because that's the only data that we have.

DR. SNIDER: Right, and there the 95 percent confidence limits are minus 14 to 51. I forget what the statisticians had to say about that. Maybe it would be useful to remind me.

CHAIRMAN DAUM: Would the statisticians like to clarify this point, please?

DR. GOLDBERG: There really isn't necessarily sufficient power for each of these endpoints, which is really the fundamental issue. It depends on how many -- I mean, I view these kinds of data in the small as descriptive; in the large, the collection of serotypes can be thought of a different way, but each one individually is just describing what your data are.

DR. SNIDER: Thank you, Dr. Goldberg.

CHAIRMAN DAUM: Thank you.

Dr. Whitley next, and then Dr. Decker, please.

DR. WHITLEY: I was going to reiterate a couple of the sentiments that had been made around the table earlier, but just to bring up one fundamental point, and that is many of us bring to this committee our own background, interest in a specific organism, and when we think about disease reduction, we think about how we can impact with a herpes simplex vaccine or an

influenza vaccine, and what we're really asked to do here, what we get hung up on is what Mimi mentioned, and that is we look at a global syndromic approach, which is not the question the Food and Drug Administration asked us.

So I think if you look at the first question and just focus on the reduction of disease caused by those serotypes, the answer to the question unequivocally has to be yes.

And then the question is: what other supporting evidence is there to indicate that that's the proper decision or not?

And I think the analyses that Dr. Pratt asked for of the sponsor clarified some of the issues about potential imbalance and potential supporting information that would lead to further iteration of that conclusion.

CHAIRMAN DAUM: Thank you very much.

Dr. Decker, please.

DR. DECKER: You know, committee members have raised a number of really interesting and provocative questions, but I think there's a clear path out of the thicket. Dixie was asking about the 19F, but let's suppose that we knew that 19F completely didn't work. I still think that that would be irrelevant because we're being asked to approve a vaccine, not serotype by serotype.

And the question, although interesting and one that deserved to be addressed in the package material if it's

true, if it didn't work, but needs to be addressed in other ways still isn't the question in front of us.

And someone -- I think it was Dr. Overturf -- earlier brought up the question of potentially inappropriate promoting of an antibiotic based on the vaccine indication, but the cure for that lies in FDA oversight and then promotion of that antibiotic and not in inappropriately failing to give the vaccine the indication that it clearly has earned.

DR. SNIDER: Can I just clarify?

With regard to Michael's comment, to me if you didn't include the serotypes, I mean, I don't want to get too nitpicky about this, but if you were talking about collectively four, 6B, 9B, 14, et cetera, then the answer is yes.

My only point is that if you are saying each one, then you don't have the data to say each one. You're talking about collectively.

DR. DECKER: Well, that's interesting because I interpreted it as the collective, but we ought to ask FDA how they want the committee to interpret it.

DR. SNIDER: That's exactly the kind of communication problems you have around this whole issue.

DR. PRATT: Well, I think even for the approval of the invasive disease indication there was not statistically significant evidence for each serotype. We considered it in the aggregate, and in the aggregate it was significant.

CHAIRMAN DAUM: Dr. Stephens and then Dr. Overturf.

DR. STEPHENS: Well, this 19F issue bothers me as well, and I am still not quite sure. The way this question reads to me we're saying that we have efficacy against 19F in this statement. That's the way I interpret this statement to read, and I'm troubled by that because I think there's not data from 19F.

CHAIRMAN DAUM: Dr. Overturf.

DR. OVERTURF: Well, you know, even being generous about the efficacy of this vaccine, if we eliminate the six and seven percent overall effect on otitis media, we're still only talking about a 50 to 57 percent effect against vaccine serotypes.

And when you look at that data specifically, the robustness on the Northern California trial is not as good because you weren't dealing with sero specific disease for most of that. So that the data is more robust for that seven percent.

So when people have alluded to using 55 percent efficacy in typhoid vaccine, which is against a disease which has a 15 to 20 percent untreated mortality rate, I don't think it's comparable to this.

So we're really talking really about a 50 or 55 percent efficacy based only on one trial which has fairly robust data and another trial which is really kind of marginal data to

make a recommendation. And I think that needs to be reminded.

The 19F issue aside, we're not talking about huge efficacy rates for what, on the other hand, even if we assume that pneumococcal disease is not a supplement to these others, it's still largely a self-limited process.

CHAIRMAN DAUM: It's been a difficult task to assess pneumococcal vaccine performance for even 60 or 70 years when people have tried to take apart each individual serotype and try and demonstrate efficacy for each serotype, and I can't remember. Maybe someone on the sponsor's team could refresh us, but for the invasive disease indication, whether every single one of the seven serotypes had proven efficacy.

My recollection is not, and yet I think the balance of the data and the prudency of the committee was to advise that the data demonstrated impressive efficacy.

So I think that if you go back even to early trials that were done before most of us and perhaps all of us were born, when you started analyzing by each specific component of the vaccine, the studies weren't powered perhaps is the right way to say it, to show individual serotype efficacy.

The second point with regard to this is that we're not really being asked to address that question when it comes time at least to sum up and say what we think, although in terms of individual comments and exploring issues here, I think it's perfectly appropriate to discuss what that's all about.

Perhaps most interesting is what's the biology of all of this because if 19F was immunogenic and produced decent amounts of antibody, how come it didn't work? That's a separate issue, I think, from deciding the question of are the data adequate to support the efficacy of this seven component vaccine against otitis media.

Other comments?

Dr. Overturf, you did say your --

DR. OVERTURF: Well, I just bring up a point that we're still hung up on the word "efficacy" because we're talking about 50 or 55 percent efficacy, again, sero specific disease, and if you use that definition, the issue is then do you have two controlled trials that really demonstrate that.

CHAIRMAN DAUM: Dr. Markovitz.

DR. MARKOVITZ: Yeah, I also agree with Dr. Overturf about this. Even if you take the generous view, this isn't the world's most efficacious vaccine, and it's also, at least for otitis media, of course, and it's not to be compared with typhoid for the reasons he alluded to.

I'm also concerned that I don't know what the proper purview is for our committee on this, but in terms of the public reaction, I mean, in the vaccine world it seems that when things don't work the way people expect them to, it can actually bode very poorly for people actually taking the vaccine and using the vaccine.

Look at influenza. There's always a lot of people who think it's not worthwhile because it doesn't work all the time, and it has a substantially higher rate of efficacy than this one does.

I don't know if that's in our proper purview to address, but I am quite concerned about that issue, that this could end up being marketed heavily for otitis media and then when everyone is still getting otitis media, there's going to be a backlash. You could end up selling less of the vaccine in the end.

CHAIRMAN DAUM: I'd be happy to hear from anyone in the agency about that, but it seems to me that it's perfectly appropriate to address that, but it's not directly speaking the questions we'll be asked to vote on.

So your comments are noted. They're in the record, and thank you.

Other comments? Dr. Glode.

DR. GLODE: Could someone from the FDA just clarify the issue of one versus two trials that speak directly to Question 1? Is there a requirement for two trials that provide data specific to Question 1?

DR. GOLDENTHAL: There's a document that's available that's called the evidence document in a general way that applies to drugs and biological products, and that document is fairly general, but it has a principle that if you have -- you

know, unless you have compelling evidence of efficacy, it's good to have two efficacy trials.

Do the endpoints have to be identical for the two trials? No.

I guess this really boils down to clinical judgment, as to, you k now, your view of these two trials. But the endpoint for the two trials do not have to be identical.

CHAIRMAN DAUM: Dr. Stephens.

DR. STEPHENS: At the pneumococcal meetings, there was some discussion about additional trials that are ongoing, and I just wanted to hear whether there is other data out there that we haven't been a part of. I was made aware of a Netherlands study that dealt with otitis media. I think there's a Navajo study that dealt with otitis media.

Are there other data that are pertinent from the perspective that would at least help us with this discussion?

CHAIRMAN DAUM: Does anyone from the sponsor want to deal with that?

DR. SIBER: Well, the buck stops there, huh? I guess it does.

(Laughter.)

DR. SIBER: There was a study in the Netherlands that was reported as an abstract in Anchorage, which we did not sponsor and which was a high risk group with recurrent otitis media at the beginning, who were given, as I recollect at least

conjugate vaccine, seven valent followed by 23 valent polysaccharide vaccine, and in that particular subgroup of individuals immunized generally at older ages with already established disease did not show any benefit of that regimen, and that's all we know about it.

It's been an abstract level presentation at this point.

The Navajo study, I would prefer if -- there's a chart? We'll know more about the details of what was done at the Navajo study.

DR. KOHBERGER: The Navajo study on otitis media was a post hoc study. Basically it's chart reviews, and I think they were just hospitalized kids; is that correct?

We think it's just hospitalized kids. So it's neither a complete ascertainment as Kaiser or a specific ascertainment as in Finland. So there's a little question there.

And just to amplify a little on the Netherlands study, it's a population of children that we'll never see in the U.S. now because they're older kids with recurrent. They were not immunized at two, four, and six.

So I don't think the Netherlands study is relevant here. Does that answer your question?

DR. STEPHENS: I agree that the data isn't in. I just wanted your comments on those two. There are other studies.

The larger question is: is there going to be

additional data above and beyond what we currently have?

DR. KOHBERGER: I don't think so.

CHAIRMAN DAUM: Dr. Snider and then Dr. Overturf.

DR. SNIDER: We were shown some serological response data, and I can't remember whether that was the entire population or some subset of the population. I would appreciate some refreshment on that, as well as the comment that the sponsor might have about serological responses among children who did wind up getting acute otitis media by various serotypes.

Is there any such information available?

CHAIRMAN DAUM: A comment to Dr. Snider's question?

DR. SIBER: Could you repeat the first part? Was that directed to the sponsor?

DR. SNIDER: Yes, George. I was just asking about the serological responses by serotype, and if that data -- if we could be refreshed about whether that came from the entire population or was a subset of the population.

And I was also asking about serological responses among those who became the cases of acute otitis media from vaccine serotypes, if there was any data on that.

Jukka has done, the statistician from Finland, some analyses of serologic correlations with otitis media. Again, these were presented as an abstract in Anchorage. They were still early days in terms of the analysis.

I don't know if you want to comment on that. Are you comfortable doing that? I did in Anchorage. So we'll do it here.

DR. JOKINEN: Well, the serological data was from a subgroup analysis of 60 per group.

CHAIRMAN DAUM: Excuse me. Can you speak right into the microphone so we can all --

DR. JOKINEN: Yeah. The serological data was for a subgroup of 60 per group, but they showed similar. There was seven time points for serological data during the FinOM study. They showed very similar responses as for the whole group, which was only sampled once, and os that's the first question, I guess.

And then analyzing serological correlates of protection we can see association with decreasing incidence with increasing antibody concentrations, but results varied between serotypes and not very confirmative, I mean, with regards to number of cases.

CHAIRMAN DAUM: Thank you.

Before you sit down, can you say who you are into the microphone for the transcript?

DR. JOKINEN: Jukka Jokinen, statistician from National Public Health Institute, Finland.

CHAIRMAN DAUM: Thank you very kindly.

Dr. Overturf, please.

DR. OVERTURF: Just one clarification regarding

that first question, and there's an assumption here, and I want to make sure the assumption is correct that the efficacy that we want to support is for the use of Prevnar as a four dose regimen in children less than two years old.

So we aren't acknowledging any data that I have seen that really supports the use as a single or in reduced doses; is that correct?

CHAIRMAN DAUM: Someone from the agency? Dr. Pratt.

DR. PRATT: Yes, that's correct.

CHAIRMAN DAUM: Okay. Dr. Parsonnet.

DR. PARSONNET: Yes, I just also want to echo that I agree with Dr. Overturf, but I had a few other comments.

One is that we are talking about an efficacy of in the 50s, but in fact, the efficacy might be lower than that because the 95 percent confidence interval goes substantially lower than that.

So 50 is the middle, but it could be lower and it could be higher, and it would be nice to have supportive data to say which end of that number it really is.

And there is really only one study that directly addresses that question. With that, the second study supports it very strongly. I mean unless we think that this vaccine is having some nonspecific effect, and I think most or at least I would believe that its effects are due to the serotypes that

we're seeing.

So I think there is only one study that directly addresses this, but the second study does show pretty strong support that this is likely to be the case.

But I think the problem that I feel like we're saying is that it's the problem with the indication, not with the efficacy again that keeps coming up, and that, you know, I just want to state for the record that I would prefer to address this point with a different indication that was being proposed because I think there are ways to address the ambiguity that we're feeling a little bit better in the overall statement that the FDA is planning to make and ways to address it in the text that follows that indication.

CHAIRMAN DAUM: I'd like to propose that we handle this because I think that it is a concern of a number of committee members and temporary voting members, that we handle this when we do formally vote by addressing the question we've been asked by FDA, but then you're welcome to make the distinction you just made and the comment to go with your vote.

Is that acceptable to FDA as a way to proceed?

DR. GOLDENTHAL: Yes.

CHAIRMAN DAUM: Okay. Additional comments that haven't been raised in discussion so far that people would like to air out a little bit?

(No response.)

CHAIRMAN DAUM: Well, we may be able to vote then. Let's try and do that and see how it goes.

We're going to -- well, you never know -- we're going to consider the first question first, and I don't think we need to have them read again. We had them read by Dr. Pratt, eloquently read after lunch, and, Dr. Stephens, we will call on you first to address question one.

I have two incoming comments here. One is from Dr. Griffin who says yes in two parts. Yes, would you please address both parts in one second?

Oh, when people are finished speaking, would they mind just pressing the little red button? Thank you.

Dr. Stephens.

DR. STEPHENS: The dangers of being at the end of the table.

CHAIRMAN DAUM: It does not happen randomly.

DR. STEPHENS: Yeah, right. I appreciate that.

(Laughter.)

DR. STEPHENS: We'll talk to you off line.

Obviously Prevnar has been very successful as a vaccine preventing basic disease. We've certainly seen that in our population, and it's been remarkable, as was mentioned earlier.

I do tend to view this somewhat as seven vaccines in one, and in general though the vaccine is safe. I think the

data, at least the Finnish data, support a 50 percent decrease in culture confirmed pneumococcal otitis media for 6B, for 14, 23F, and 18C, and probably also for 9V and four, and both studies demonstrate an overall efficacy of approximately six percent against otitis media.

And there's also obviously reasonably convincing data that there is significant decrease in tube placement and potentially in complications.

And I think there's also evidence that 6A and 23A and 9N are probably also affected in terms of limited data by the vaccine.

I have concerns about 19F. I'm not quite sure that we have demonstrated that the -- the efficacy is at best very limited for 19F, and I share Dr. Parsonnet's view that maybe this could be handled differently than the statement as worded as the better approach rather than the specific statement.

I am concerned also about the serotype replacement issue.

So with all of those caveats, I will vote a qualified yes to the first part, and it doesn't look like we're going to get any additional data of significance.

CHAIRMAN DAUM: I hate to boomerang this back to you, but I don't think we can have qualified yeses. We need a vote, with the comments being qualifiers as appropriate.

DR. STEPHENS: So moved and seconded.

(Laughter.)

CHAIRMAN DAUM: Thank you, sir.

Dr. Katz.

DR. KATZ: I don't think I have anything different to say than David Stephens has said. The question as it is worded, we're not voting on the wording of what was given to us as the statement to be made on the vaccine insert or the package. We're just voting on are the data adequate to support efficacy, and I would vote yes.

CHAIRMAN DAUM: Thank you very much, Dr. Katz.

Dr. Snider.

DR. SNIDER: With regard to the answer to question one, my answer would be yes. I would have many of the reservations or concerns, I should say, that Dr. Stephens has articulated and would also be with those around the table who have expressed some concerns about whether this would be a wise thing to do to include this indication, and whether that would be good for the vaccine, good for the manufacturer, society at large, at least as it's now articulated, and would encourage further thought in terms of how the indication would be laid out, as well as what kind of physician education and parent education program would be put in place so that people understood what they could expect and not expect from the use of this vaccine.

Because I do worry about many of the secondary and tertiary consequences that people have already mentioned that I

don't need to go back over.

CHAIRMAN DAUM: And your vote is yes, Dixie?

DR. SNIDER: My vote is yes. Yeah, I tried to start out and make that clear.

CHAIRMAN DAUM: You probably did. I'm sorry.

Dr. Hamilton.

DR. HAMILTON: I believe the data are sufficient to support efficacy.

CHAIRMAN DAUM: Can I stop you? Just speak right into that microphone so that we can hear. Pull it toward you.

There you go.

DR. HAMILTON: I think the data are sufficient to support efficacy as the question is phrased. I think I'd be interested in looking at the serologic response of the 60 individuals who developed 19F infection. Whether that would be of any use or not I don't know, but that does seem to be an outlier.

CHAIRMAN DAUM: Thank you.

Dr. Schwartz.

DR. SCHWARTZ: Yes.

CHAIRMAN DAUM: Succinct.

Dr. Glode.

DR. GLODE: I'm going to vote no. I think the data support efficacy from the Finnish trial, serotype specific efficacy. I'm simply not willing to presume from the Kaiser

trial that that's the explanation for the reduction, and I only have the ruptured eardrum information, which is not statistically significant.

So I think that I'm voting no, not because I don't believe the Finnish trial, but on the basis of just one trial that proves that to me.

CHAIRMAN DAUM: Dr. Glode, we have to ask you part two since you voted no. No deed goes unpunished here.

Would additional analyses derived from the trial or additional clinical trials be useful in establishing efficacy?

DR. GLODE: I don't think any additional analyses would be helpful because it looked like they have been thoroughly done with both trials. Certainly another tympanocentesis trial looking at vaccine specific serotype would be helpful.

CHAIRMAN DAUM: Thank you very much.

Dr. Overturf.

DR. OVERTURF: I also have to vote no because of the same reason. I feel that only one trial, the control trial, has really demonstrated efficacy.

I also am very concerned that a yes vote here sets another precedent which we haven't talked about. One is besides establishing some arbitrary definition of, quote, efficacy, unquote, for a noninvasive disease, it also would, it seems to me, establish a new bar that you must show efficacy for every indication you list, including sinusitis, pneumonia, and other

issues.

So actually I still like the recommendation of Dr. Parsonnet, which is that if you're going to do this, if you do it intuitively, you do it based upon all diseases due to pneumococci of the serotypes.

I agree with Dr. Glode that probably the only thing that's going to resolve this is another tympanocentesis trial. It's the only thing that's going to really confirm what I believe is probably a correct observation from the Finnish trial.

So my vote is no.

CHAIRMAN DAUM: Thank you very much.

Dr. Faggett, sir.

DR. FAGGETT: Yes. I do have some concerns that the studies presented are not as inclusive as I would like to see in terms of having the broader, heterogeneous American population represented.

And I do have some reservations about efficacy with 19F.

Having said all of that though, I think in terms of the data adequate to support efficacy of Prevnar in infants and toddlers, I think we do have adequate data to support efficacy because we're not saying just how much.

So I think I'm going to go ahead and vote yes on this, with those reservations.

CHAIRMAN DAUM: Thank you.

Dr. Griffin.

DR. GRIFFIN: I'm going to vote yes, and just state that I think the Finnish trial, as many people have said, I think gave us definitive evidence of efficacy against these serotypes. The fact that the overall effect on otitis media was almost exactly the same as it was in the Kaiser trial, you would have to invoke a thought that it was a totally nonspecific effect and that there wasn't an effect on these same serotypes, that it didn't have the same sort of display of different types of causes of otitis media.

So I think the data is adequate and I think it has been shown in two trials.

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

Dr. Whitley.

DR. WHITLEY: My vote is yes for virtually identical reasons to Diane's, and that is I think unequivocal evidence of efficacy was established in the Finnish study, and I think it's unreasonable to think that the results from the Kaiser Permanente study could be attributed to anything other than the vaccine.

Having said that, I do think it's important for both the agency and the sponsor to carefully weigh how the package insert reads and whether we go back to what Sam's recommendation was earlier regarding the lesser degree of efficacy in the prevention of otitis media or careful words to

indicate that that would be the case, I think, is relevant because we clearly don't want to detract from the impact of this vaccine on prevention of invasive disease.

CHAIRMAN DAUM: Think you, Rich.

Dr. Diaz.

DR. DIAZ: I likewise would vote yes because I am also willing to extrapolate the Finnish data into the Kaiser trial. The data is so similar, and yet I do agree that only another tympanocentesis study would validate that completely for me.

But the extrapolation is there. As Dr. Griffin pointed out, you'd have to imagine something completely unrelated would have played into making the data become or be the same in the Kaiser trial.

That having been said, I think one of the points that Dr. Katz raised earlier, which is that we're not being asked to validate or vote for a package insert as stated in the materials that we received, is extremely important because I, too, have great concerns and reservations about issues surrounding package insert for this indication for all of the reasons that everyone has already elucidated.

CHAIRMAN DAUM: Thank you, Dr. Diaz.

Dr. Goldberg, please.

DR. GOLDBERG: I'm voting yes as well.

That said, I really view the otitis media

endpoints here as secondary endpoints to the basic indication for the vaccine, and I urge the agency to find a way to deal with this and not call it an indication in the label; that there needs to be another mechanism for handling this that takes into account the primary purpose of giving the vaccine where the major impact is felt and doesn't detract in the long run from that.

CHAIRMAN DAUM: Thank you.

Dr. Markovitz.

DR. MARKOVITZ: Yeah, I think the way the question is phrased I have to vote yes because I think there is efficacy within this narrow spectrum.

I have reservations that have already been expressed by me and others here and I might return to on question two, but for question one I would say yes.

CHAIRMAN DAUM: Thank you.

Dr. Parsonnet.

DR. PARSONNET: I say yes, and I just also want to point out that I don't think there's much experience with what the efficacy should be for a disease that's not invasive and not produced by a toxin. So it may be that 50 percent is really fantastic for a noninvasive disease and we just don't know from our experience yet what noninvasive disease efficacies are ever going to be.

And with that I just want to reiterate my thoughts about the labeling, that I'm concerned about the labeling as we

talked about before.

CHAIRMAN DAUM: Thank you.

Ms. Fisher.

MS. FISHER: As I understand it, the function of the FDA standards for including a use indication in a vaccine manufacturer's label is to insure truth in advertising. The public looks to the FDA and trusts that CBER protects their right to informed consent when using biological products.

We've been asked by Prevnar's manufacturer to agree they have proven efficacy for prevention of otitis media, which would then allow the advertising of Prevnar as a vaccine to prevent otitis media even though a large U.S. study has shown only a seven percent reduction in all otitis media cases.

Practically, that means that 93 percent of the children whose mothers believe Prevnar is an ear infection vaccine because the label says so, 93 percent of these children may be susceptible to otitis media even though they've been vaccinated.

Seven percent is not a scientific standard for vaccine efficacy for a specific condition that engenders a lot of trust. Because apparently there is no room under the regulations to simply state that Prevnar efficacy with respect to presenting otitis media has been shown to be seven percent, which would be the most truthful and accurate labeling.

I must vote that efficacy has not been established

to justify the labeling change, and I don't think the manufacturer should spend more time and money trying to prove efficacy for otitis media in light of these studies and should be well satisfied with the use of Prevnar to protect against severe invasive disease.

CHAIRMAN DAUM: Thank you, Ms. Fisher.

I guess I'm probably last and possibly least, but a couple of comments.

I think that I'm going to vote yes for the question the way it's worded. I think this vaccine represents a real triumph for children in this country. It's had a wonderful track record in terms of its safety profile, and as important, a wonderful impact on invasive pneumococcal disease.

I believe that the two trials that were done, although I agree with Dr. Glode's comments about the differences in methodology and conclusions that can be draw from each one of them are internally consistent, and they do show that there is efficacy against otitis.

A plausible secondary part of that is for me the more severe the otitis was, the better the vaccine seemed to perform. I'm not troubled globally because of a lot of previous work that's gone on in this field that there isn't efficacy shown for every single serotype. I think that the problem of powering the study to do that would be formidable.

I do have some concerns though. One of them is

that by saying yes to the demonstration of efficacy that we somehow have established or influenced the agency to establish a candle for equivalency or noninferiority of other vaccines to these numbers, and I have some concerns about that.

I'm disappointed that the vaccine isn't more efficacious. I think my answer is, yes, it is, but I wish it were higher, and so that I share some of the concerns by Dr. Parsonnet, Ms. Fisher, and many others that this number be translated into an important clinical message.

I'm concerned about the point of Dr. Overturf, that even when you put the best possible light on things and take only culture proven otitis due to serotypes contained in the vaccine, that the efficacy was still only in the 50 percent range, and I think that raises some points that we haven't said much about, and that is that we don't completely understand the biology of preventing otitis media.

The 19F story is instructive to me only in that it says that there isn't a simple relationship between the production of antibody and efficacy in this case. I don't know what the other issues are. They could have something to do with cytokines or something to do with individual eustachian tube kinetics or lots of other issues, but I think this is more than just measuring antibody and looking at efficacy, and that's why I think in the best case we only got to in the mid-50s.

Having said that and voted, and to emphasize I do

vote yes about efficacy, I would offer the extraneous advice or probably unwelcome advice that this not be used to translate into promotion, sales marketing, or pressure on the public to accept the vaccine based on this performance alone.

I think there are many other reasons to promote and use this vaccine, and I think that it has been said repeatedly, and I think that it's recommended for all U.S. children as it should be, and I think that should continue to go on.

But I personally would not like the efficacy that I believe has been established to be translated into detailing or advertisements or direct marketing to the public about the impact of this vaccine on otitis media.

And with that, I think I'm done.

I'd like to move on at this point to announce the vote for question one. Sorry. One second.

Dr. Decker, you need to state your opinion, but I think you already have. Did you want to say something else about question one? I'm pretty sure you've done it.

The outcome on the vote on question one is 13 voting in favor of the data being adequate to support efficacy, three opposed, 13 to three.

The second question isn't really a question, but is a discussion point that we would like to hear or the agency would like to hear committee members weigh in on specifically.

I normally start off with some general discussion before we go to the specifics, but my sense is we've had the general discussion. If anyone disagrees with me, please let me know, but I'd like to start with Dr. Stephens again and just address -- perhaps we can do this fairly briefly -- the issues in question two, but please feel free to make whatever points you wish.

DR. STEPHENS: I think a lot of this has already been stated. I'd like to make two points.

One is the issue of 19F and an urge. Continue work on trying to understand why 19F is, in fact, not working very well in current vaccine.

Secondly, I think pneumococcal disease is a moving target, and what is efficacy now with the serotypes in terms of prevention of otitis media may not in five years, given serotype replacement and other issues be efficacy.

So there needs to be continued monitoring of post marketing, and a continued look at otitis media.

CHAIRMAN DAUM: Thank you very much, David.

Dr. Katz.

DR. KATZ: I would like to emphasize what Dr. Parsonnet had, and that is otitis media, even due to a single bacterium, is not a single etiologic relationship. We know that preceding viral infection; we know that allergy; we know that smoke inhalation; there are many factors that have to do with

this, and to expect that a vaccine against a bacterium is going to change things 80 percent is naive.

And I think that we need to continue to support research in all the areas relating to the etiology, not just the pneumococcus in the reduction of acute otitis media episodes, and therefore, I'm comfortable with saying that what we voted, with question number one.

I would be uncomfortable, as has been repeatedly stated to say that, "Okay, folks. Now we've got the panacea for otitis media. Have your children immunized not to prevent invasive disease, but to prevent otitis media."

And I think a lot needs to be done in research. You used the term or Diane did "syndromic." And I think we would be less than a good Advisory Committee if we let it go as just we've solved an issue.

We need a great deal more to be studied. I think one of the side benefits that I hope might come from this, of course, and this might be studied particularly in the Kaiser population, is reduction in the use of antibiotics and antibiotic resistance because I think those are probably more major questions than otitis media.

CHAIRMAN DAUM: Thank you very much.

Dr. Katz raised many good points.

Dr. Snider.

DR. SNIDER: Well, with regard to acute otitis

media episodes caused by Streptococcus pneumoniae, regardless of serotype, I mean, obviously efficacy drops. I mean, that's pretty clear, although, you know, some of the related serotypes, that data, although as Dr. Goldberg has pointed out are only anecdotal in the sense that they're not definitive and not statistically significant. They're encouraging.

But overall, as one would expect, there's not a huge amount of efficacy against serotypes that are not included in the vaccine, nor should we expect there to be.

Like others, I think that we -- I think David mentioned this -- we need to be vigilant because doing this trial in one setting, in one country, at one particular point in time doesn't necessarily give us a clear indication what might happen when the vaccine is used in larger populations in different places, at different times, and so forth.

So I think we need to be vigilant around this issue of potential replacement. I don't think it's completely off the table that it will occur or won't occur, and the issue of drug resistance, the story seems promising right now in terms of potential for using this vaccine to reduce the number of drug resistant cases of pneumococcal acute otitis media.

But we need to monitor over time to make sure that that's not just a phenomenon that is a result of particular circumstances that exist now or exist -- but won't exist in the future.

I was a little surprised with regard to tube placement not being different early in the trial and showing a difference only later on, but I think we had some explanation given to that that sounded reasonable.

So I think there is a lot more work that needs to be done to try to understand this disease, to try to understand this vaccine, to try to understand why certain -- it seems to protect against certain serotypes better than others. One would hope that the whole pneumococcal conjugate story would continue to evolve with more serotypes in subsequent vaccines down the road, and that we'll continue to be discussing this as new data become available, as newer pneumococcal vaccines become available.

CHAIRMAN DAUM: Thank you, Dixie.

We'll move on, please, to Dr. Hamilton.

DR. HAMILTON: You requested the strength of the data, but not in which direction.

CHAIRMAN DAUM: Dr. Hamilton, will you speak right into the microphone so that we can be sure we hear you?

DR. HAMILTON: Okay.

CHAIRMAN DAUM: Thank you.

DR. HAMILTON: You've requested the strength of the data, but the question does not refer to which direction you're interested in.

CHAIRMAN DAUM: Your choice.

DR. HAMILTON: Okay. Acute otitis media caused by S. pneumonia regardless of the serotype, certainly the Finnish study suggests that the serotype related strains, there's some efficacy going from 56 to 34, but for those that are not related at all, there doesn't appear to be any efficacy.

And then it's kind of like the top of a pyramid that branches out. As you get to the syndrome at the bottom, you get less and less effective, and one of my queries is actually whether that 56 percent and 34 percent reduction directly correlates into the six percent reduction or you're seeing replacement with other radiologic agents there.

And no other microbiologic data was mentioned, but I'd just be curious to know.

Overall reduction, acute otitis media episodes because it was supported by two trials, although somewhat differently done. I think the strength of the data is pretty good.

Frequent otitis media, I would say no, and tympanostomy tube placement I would say no. I agree that the tympanostomy tube replacement was not adequate and well controlled, and it's impossible to determine how one would relate one to the other, given the different time frames and the different treatment methods.

The other thing that you haven't mentioned here but I think is provocative is the rupture issue out of Kaiser,

and I would like to know a little more about the microbiology there, whether they were doing microbiology for, say, Group A strep. with those who ruptured.

CHAIRMAN DAUM: Thank you very much.

We're going to go out of sequence here and ask Dr. Decker to comment next.

DR. DECKER: Thank you, Bob.

CHAIRMAN DAUM: Because he has to leave.

DR. DECKER: You know what I was struck by more than anything else, I think, in looking at these data was the remarkable consistency of the data when you recognize the usual statistical limitations and variations, particularly with declining sample size. What you see is a remarkably consistent picture, I think, of efficacy.

Let me put it this way. Were it known without question that the vaccine were efficacious against the serotypes that cause otitis media and it was reducing otitis media, then you would see the pattern of results that we have here, and apart from the limitations caused by shrinking sample size as questions become more narrow, the variability caused in each statistical sampling and the fact that not all serotypes are equally prevented, with those thoughts in mind, the data are remarkably consistent.

And i think the questions that the data really leave for us aren't necessarily the ones listed here, but rather

some of the questions that have already been brought up, the 19F question and what's going on with that. Why is it behaving differently? The serotype replacement question begs further attention.

To me most of the questions that are asked in item two, although perhaps not proven statistically with these data, clearly are addressed so uniformly and so consistently that I'm not concerned by them.

CHAIRMAN DAUM: Thank you.

We'll continue going in sequence now. Dr. Schwartz, I don't think you can be quite as succinct this time as last time.

DR. SCHWARTZ: No. Everything that I can think of that's been said has been said with one exception. There are actually two different vaccines, and I know we're not discussing the other vaccine that was tested in Finland, and to me that means that there are, in fact, two trials. Even though the vaccine is a different manufacturer and a different carrying protein, we don't have any information at all as to how effective was the Merck vaccine, the septavalent vaccine.

Just for curiosity, did that do the same thing? And if so that would bolster my confidence that I voted the right way.

CHAIRMAN DAUM: Does anybody from the agency or the manufacturer wish to comment on that question? You have the

right to remain silent.

DR. GOLDENTHAL: I don't think it would be appropriate for the agency to comment, but I do see a representative from Merck.

CHAIRMAN DAUM: We also have an investigator at the microphone.

DR. KILPI: All right. The other vaccine, we have presented the results for the other vaccine at several conferences, and it provided almost equal protection against AOM due to vaccine serotypes. The point estimate was 56 percent against the overall vaccine serotypes.

It also had a problem with 19F. I think the point estimate was 34 or 37. I'm not quite sure, but overall the efficacy against the vaccine serotypes was pretty much the same.

However, the point estimate in the prevention of any pneumococcal AOM was slightly lower. The point estimates was only 25 percent.

CHAIRMAN DAUM: Thank you very much. That's very helpful and very interesting, and I'd like to just remind the committee though that it's not part of what we're considering at the table today.

Dr. Glode.

DR. GLODE: I think that the table on page 29 of Dr. Pratt's handout summarizes this information very nicely, and it pulls it all together.

So acute otitis media caused by Strep. pneumoniae, regardless of serotype, again, the single study that answers that is the Finnish study with 32 percent reduction, lower limits of confidence, 20 percent, efficacy. Sorry.

Overall reduction in acute otitis media, again, as already mentioned, statistically significant in the Kaiser trial, in the same range in the Finnish trial, but not statistically significant due to lack of power to detect that apparently.

And then effect on frequent otitis media, again, summarized in the table. The most relevant data there would come from the Kaiser study.

In tympanostomy tube placement, I remain confused about whether or not there was adequate power in the Finnish study to show it, and if there was why it didn't confirm and validate the Kaiser study.

So I think that at least with tympanostomy tube, I'm still a little confused about that issue, and overall reduction in acute otitis media I can explain that by a power of the study.

I did think between these times of one other analysis that would be of interest to me and was probably done, and that addresses the issue of should you presume that the only explanation for the reduction of overall otitis media in the Kaiser trial has to be related to the effect of the vaccine on vaccine specific serotypes because I have been impressed for a

number of years with the biologic cross-reactions between organisms, in particular, pneumococcus and Haemophilus.

So it would be of interest, and I'm sure people have already done this, to just look at the efficacy or lack of efficacy against Haemophilus otitis and Moraxella otitis in the two groups.

CHAIRMAN DAUM: That was a provocative comment. Thank you, Mimi.

Dr. Overturf.

DR. OVERTURF: I think I agree with most of what's been said. In particular, regarding episodes caused by Strep. pneumo. regardless of serotype, I think it's clear that there is very little, if any, efficacy, and this is actually supportive of the vaccine against serotypes not contained within the vaccine.

And I think the issue of replacement serotypes is an important issue for this disease, and it's probably going to be the same problem for Haemophilus and other otitis media vaccines in the future.

And one of the concerns I have is once the vaccine is approved for this indication, how demanding is the post marketing surveillance going to be in terms of watching for this?

Today we have a six or seven percent reduction in otitis media if you believe the data now. Will it be three and a half percent next year and will it be less than that thereafter?

Because we will be setting a new baseline here,

which will be established by the routine immunization of all children less than two years of age in this country with this vaccine.

So I think that's going to be an issue about future overall reduction in acute otitis media episodes. And eventually if frequent otitis media is really more due to pneumococcal disease, that also will be an issue.

I have the same concerns about the tympanostomy tube placement. I don't think I'm clear because I think this is a disease which probably is related to a lot of other issues that can't be directly identified in the study, particularly issues of individual anatomy genetics, other risk factors, and also just the indications and use of tympanostomy tubes.

So I think it may be at some point appropriate when you do further studies to move this particular indication up the ladder a little bit so that one moves it up to a primary outcome rather than and with more restrictive indications because I think right now it's not clear to me that the way it was examined in the current studies really makes it clear that the outcome was affected by the vaccine or affected by some other factors that we couldn't really identify.

CHAIRMAN DAUM: Thank you very much.

Dr. Faggett.

DR. FAGGETT: I pretty much agree with my distinguished colleagues and their comments. Specifically the

acute otitis media episodes, question A, the Finnish study does have good evidence of efficacy. Kaiser is equivocal.

Question B, overall reduction in acute otitis media, there is some evidence of efficacy.

Question C, frequent otitis media, still equivocal. Some evidence of efficacy.

And, again, pretty much the same with the PE tube placement.

I would hope that further studies would allow us to have the same kind of eloquent data in terms of looking at the broader population so that we can, indeed, draw more conclusions for the population that is not included in this study at the present.

CHAIRMAN DAUM: Thank you.

Dr. Griffin.

DR. GRIFFIN: Okay. I think that the two studies, because of their very different design, shed light on different ones of these questions, more or less light on different ones of these questions.

In the first, you're talking about acute otitis media caused by all serotypes of S. pneumoniae, and in a way that's just making it less specific and so diluting out the effect somehow by adding in all of the serotypes.

And I think there is statistically significant evidence from the Finnish study that that happens, that you still

have a significant effect even with that dilution.

I think the issue of replacement serotypes is an important one, and I think it's also an interesting one because it isn't clear to me. I mean, these serotypes were chosen to make a vaccine partly because they cause most of the disease.

And so are those replacement serotypes intrinsically less virulent and, therefore, even though they may appear more, they still won't cause more severe disease or not, and I think time is only going to tell what that answer is.

The second on the Part B, those studies showed a very similar decrease in overall reduction, one, because the power of the study is not statistically significant while the other of the Kaiser study is.

Again, with frequent otitis media, because that was an outcome where there were larger populations in the Kaiser study, there was a significant difference there.

Like everyone else, the tympanostomy data is somewhat confusing, although I thought the Kaiser data for an American population using what's pretty much a real world situation did indicate that there will be a reduction in tympanostomy tube placement.

CHAIRMAN DAUM: Thank you very much.

Dr. Whitley.

DR. WHITLEY: I really don't have anything to add to the discussion that has taken place. I just reiterate four

points:

That if the FDA has a chance to do Phase IV studies with the sponsor, they would be important, and clearly replacement serotypes and the response to 19F are critical, but also the whole issue of understanding better antibiotic usage in this targeted patient population, the propensity to develop resistance or not develop resistance becomes essentially important.

CHAIRMAN DAUM: Thanks.

Dr. Diaz.

DR. DIAZ: Thank you.

Just a couple of comments in general. I'm not surprised with the delusional effect as has been described as one moves from specific serotypes to, you know, related serotypes, to nonrelated serotypes, to acute otitis media as a whole. It follows logically, and I think the data followed logically.

It is a specific vaccine in the sense that it has certain serotypes within that vaccine.

I do think though that this issue that's been raised about replacement serotypes is an important question, but I might even consider broadening that in wondering about not only replacement serotypes, but perhaps replacement of other organisms shift because this really is not a selective ecosystem in the middle ear for the pneumococcus per se.

And I think a lot of my colleagues have commented

upon sort of the complexity of acute otitis media. I mean, it's such a common diagnosis, such a common disease, and yet our ability at diagnosing it remains at about the same point it was years and years and years ago.

That having been said though, if all otitis media is not the same, meaning that there are more pathogenic and virulent organisms, as appears to be the case, then we should be able to see some differences or changes over time as the use of the vaccine increases dramatically in this country.

And one would hope that even if we do not see truly a decrease in cute otitis media, the seven percent versus three percent next year, et cetera, et cetera, that we might see some changes in some of the things that others have commented upon in terms of monitoring, and that might be the use of antibiotics overall, changing patterns in use of antibiotics, changes in diagnoses for febrile illnesses, more virtual syndrome versus acute otitis media per se.

And likewise perhaps tympanostomy tube placement. Some of those things can be looked at. Tympanostomy tube placements can be monitored by ICD-9 codes and a variety of other mechanisms sine they tend to be in hospital procedures, and I would encourage the utility of looking at some of these other perhaps not specific, but yet indicators of morbidity due to acute otitis media in general in the future.

CHAIRMAN DAUM: Thank you.

Dr. Goldberg.

DR. GOLDBERG: I think that one comment is that I think the trials are remarkably consistent. The places where they're not -- the only difference that I would call possibly nonconsistent is the tube placement issue, which I think various reasons for that have been alluded to throughout the morning.

All of that said, you can look at the two trials as complementary and quite supportive of one another with regard to the results. The real issue is: is this efficacy sufficient, particularly with regard to the acute otitis media overall endpoint?

In fact, would I be happier if four percent were really significantly different from zero in the intent to treat in the Finnish study? Not really. It wouldn't matter to me.

I mean, I would urge the agency to really give careful consideration to what we mean by efficacy and what is meaningful efficacy and how you deal with reporting results like this in a label without calling it an indication that can detract from the primary purpose of the vaccine.

I mean, I think that has to be considered. I mean, I think that they basically in one way or another -- some efficacy, in quotes, or activity with regard to each of these endpoints has been demonstrated in one or the other or both of these trials. The issue is what to do with it.

CHAIRMAN DAUM: Thank you.

We are going to address the issue of how to communicate information based on your beliefs today when we finish addressing question two. So I'm glad you raised that point, and we'll come back to it.

Dr. Markovitz.

DR. MARKOVITZ: Yeah. I don't have too much to add, except that if we could make question two a yes or no, I'd have to say no. I'm not very impressed with any of the other efficacy of this vaccine beyond what was asked in question one.

And I'd like to echo the comments just very quickly of several of my colleagues. Actually Dr. Goldberg, who I know is a statistician, has correctly pointed out, I think, that just having a good P value doesn't make something really clinically useful and worth marketing.

And then I'd like to also agree with Ms. Fisher in terms of the possibility that by marketing this for otitis media we'll squander the good name of the vaccine and hence do much more harm than good for both the public and, frankly, for the company, too

And then lastly, I'd like to agree with Drs. Parsonnet and Katz that some rewording would be very much in order when it comes to the indication, and that might solve the problem.

Thanks.

CHAIRMAN DAUM: Thank you.

Dr. Parsonnet.

DR. PARSONNET: Yeah. I don't have very much to add to the things that have already been presented, that these particular secondary outcomes have not been as well demonstrated, but I think one of the things that I think from a philosophical perspective it's important to think about is, again, that this is a vaccine. We don't typically have vaccines against such a common resident of our normal flora. This is something that people carry a lot and very frequently, and I don't think that it's possible to really predict what the long-term consequences of trying to address that with a vaccine is going to be in terms of the disease outcomes that might be associated with it that may be replaced by other pneumococci, may be replaced by other organisms, may have effects that we just don't really know.

So I would encourage since we are changing the human ecology here, that people really look at it very carefully and address this after marketing.

CHAIRMAN DAUM: Thank you.

And Ms. Fisher.

MS. FISHER: Well, a five to 21 percent reduction of these secondary otitis media outcomes is not strong evidence for proof of efficacy for this condition, and I do think that more data needs to be generated regarding the possible future increases of otitis media due to serotypes not covered in Prevnar as a result of mass use of Prevnar.

CHAIRMAN DAUM: Thanks a lot.

Dr. Midthun, you wanted to ask the committee to address an additional issue informally. Could you tell us what it is?

DR. MIDTHUN: Yes. I'd really appreciate input from the committee members on how they would suggest communicating this information to the prescriber because I've heard a lot of concerns about how this might be done, and we're really appreciate input on that.

The other thing I would like to speak to, Dr. Daum, is you made a comment that you had concerns about how perhaps some of this information might be used for marketing purposes, and I just wanted to come back to say that information that is included in the package insert can be used for marketing, promotional labeling, but that is something that is reviewed by FDA and has to be approved by us, but that is something that is done.

CHAIRMAN DAUM: Okay. So I would be happy to have comment on this question from people who -- we don't need to hear from every single person, but people who want to address this question, fine.

Maybe, Ms. Fisher, I'll bet you have a comment on this. Would you like to start?

MS. FISHER: Well, I think my comments probably have covered that territory.

CHAIRMAN DAUM: Okay.

MS. FISHER: I think we have to be extremely careful about how this vaccine is marketed because I do think it will result -- it could possibly result -- in the compromising of trust in the labeling that the FDA puts on the vaccine.

CHAIRMAN DAUM: Anybody else?

Dr. Parsonnet, we'll just go around. Welcome to pass or comment, as you wish.

DR. PARSONNET: No, I don't have anything to add. I think, again, being less specific about the indications, about what specific things that Strep. pneumoniae causes or saying to a lesser extent this affects otitis media, either of those or some other alternative of that would be fine.

DR. MARKOVITZ: Yeah, I'd agree with dr. Parsonnet.

DR. GOLDBERG: I would agree with the comments that were just made.

DR. DIAZ: The same.

DR. FAGGETT: Yeah, I kind of agree with previous comments. I think some wording like the vaccine with its proven efficacy against invasive disease is also useful against otitis media. I think something like that would be a possibility.

DR. OVERTURF: It would seem to me that there's a requirement here for the manufacturers who are going to accept the responsibility for disseminating this information also to

disseminate effective education.

And because this is going to be a requirement, patients will come in and ask for the otitis media vaccine, and I think that's going to have to be explained.

I think the efficacy that we have said we'd demonstrate is going to have to be explained, and people are going to have to have realistic interpretation of this.

So I think in addition to how you label the vaccine, the educational component is going to be extremely important here. Part of that starts with the labeling of the vaccine, but it's going to require one step further as well.

I think also certain kinds of venues for marketing of this vaccine with this indication are probably not appropriate, and I don't think they should be approved, such as direct marketing. I think that would be a mistake because it doesn't give the practitioner the opportunity for the educational piece.

CHAIRMAN DAUM: Mimi, comments?

DR. GLODE: I could see things going wrong in two directions. If a parent -- again, if the educational system wasn't as it should be and someone said, "I really don't care about this vaccine for my child. I barely know what meningitis is, but I sure want it for ear infections," that's a disservice to the country and to the children in the country.

Similarly, if it's marketed in any way as an

otitis vaccine and then loses credibility because it doesn't prevent otitis in the majority of children, that's a disservice. If in any way it inhibits one single parent from getting it to prevent meningitis and serious invasive infection. So I'm worried about that.

DR. SCHWARTZ: I would like to recommend that as part of post marketing, if it's at all possible, when any company does studies that involves tympanocentesis, to have a central repository for pneumococcal isolates to have serotyping done because that's not usually done for studies of acute otitis media; only identification of the organism and not serotyping.

But the only way we're going to know is by having those investigators who are adept at and perform usually for study purposes tympanocentesis to have such a central repository to keep tracks on what is happening with the serotyping of the isolates that we get from the middle ear.

DR. HAMILTON: I think one of the difficulties with the claim is that it's not in gray, but it's totally in black and white, protective against otitis media caused by S. pneumoniae. If that could be accompanied at all points by a statement that describes the amount of otitis media that's caused by S. pneumoniae against the vaccine would be effective. For instance, all pneumococcal isolates, vaccine related pneumococcal -- this is too complex for a label, but I think the public could understand a five percent reduction in otitis media because that

is what is caused in the studies by capsular serotypes, represented in the vaccine.

DR. SNIDER: Dixie Snider.

The scientist part of me says that it is appropriate to communicate to physicians certainly that the vaccine has demonstrated efficacy in the range of, well, 57 percent efficacy against the serotypes that are included in the vaccine, and that overall reduction of six to seven percent in the incidence of acute otitis media have been observed in two trials or something to that effect.

I guess there's another part of me that is a public health policy type who wonders if going beyond that is really wise, and I have concerns that others have expressed certainly about direct marketing, but about really promoting this even to physicians who are overwhelmed, and certainly to parents to give the impression that it's some sort of panacea for acute otitis media.

So I'm very much in favor of communicating accurately the scientific information to physicians that wouldn't object to communicating it to parents along the lines that Dr. Hamilton just mentioned. But I have some real concerns about going much further with this information.

CHAIRMAN DAUM: Dr. Katz.

DR. KATZ: I'm surprised Dr. Snider didn't say what I was going to say, which is that there are three groups who

spread most of the information about vaccines in this country. One is the Committee on Infectious Diseases of the American Academy of Pediatrics. One is the Advisory Committee on Immunization Practices of the Centers for Disease Control, of which Dr. Snider is the Executive Secretary or something like that. And the third is the Committee of the American Academy of Family Physicians.

I think that they are very knowledgeable, very judicious individuals, the members. I feel quite confident that they will not alter their recommendation statements to say that this is a vaccine for otitis media.

In fact, I hope that in their next statements about the vaccine, they may say there may be a fringe benefit of this vaccine which we recommend universally for children to prevent invasive disease, that maybe it reduces otitis media by six or seven percent, but that its primary justification for use is to prevent invasive disease and not to be fooled by thinking of it as an otitis media vaccine.

So I am not worried about the educational aspects because I think the groups, the responsible groups who promulgate vaccine recommendations and to which 55,000 pediatricians and a 100-plus thousand family physicians listen very carefully, will not push this as an otitis vaccine.

CHAIRMAN DAUM: Thank you, Dr. Katz.

Dr. Stephens.

DR. STEPHENS: Being last this time, I --

CHAIRMAN DAUM: I'm last.

(Laughter)

DR. STEPHENS: Almost last, that's right.

I agree with almost every comment. I think it is a mistake on the part of the company and the FDA to market this as an otitis vaccine, otitis media prevention vaccine.

I think that the package insert should try to deal with this issue in a way, separate from a clear indication that this prevents otitis media.

Whether that be the epidemiology section or another section, I appreciate the comment that you don't like to do that, but I think in this instance it might be worthwhile reconsidering.

CHAIRMAN DAUM: And as the last person, I would just like to emphasize and elaborate slightly on some of the points that have been made.

In addition to the groups Dr. Katz mentioned as formulating policy and reaching consumers and providers, there is, of course, a fourth group and that is the media. And I think that what this vaccine, that road was already started down when it was first licensed. There are a number of media contacts by myself, and I'm sure many others at this table, about the new vaccine that has just been licensed that prevents otitis media.

I think we are coming full circle now and visiting

it with actual data, data that have been published and are already available in the medical literature, by and large.

I am very worried that the notion go forward from this meeting that we have established today that this vaccine prevents otitis media to an important clinical degree. I do believe that the vote for efficacy is correct, but the overall impact on otitis media, particularly at the individual consumer level, is going to be very small.

We are already immunizing every child in the United States, at least with intent to treat in statements of committees. I just don't think that there is a reason why a child should come forward and say, "I want this vaccine because it is the otitis media vaccine."

And I would urge the company and urge the agency. I don't completely understand the process by which things are added to labels or given indications, but I would almost not push for an indication for this and I certainly wouldn't push for a marketing and promotional blitz based on what we have heard today.

I think this is important information. I agree with Dr. Katz and others. This is information to build on, understand otitis media biology better, but to be very careful about how it is represented to the public.

I don't think that we have an otitis media prevention vaccine yet.

I think we are done with the otitis media portion of today's meeting. I would like to propose that we take a 15-minute break, but before we do that let's have the open public hearing on acute otitis media, could we?

Is there anyone in the audience that wishes to speak to the committee about acute otitis media?

(No response.)

CHAIRMAN DAUM: That being the case, we will take a 15-minute break and reconvene at exactly 2:45.

(Whereupon, the foregoing matter went off the record at 2:37 p.m. and went back on the record at 2:48 p.m.)

CHAIRMAN DAUM: Okay. We would like to call everyone to order, please.

The next item on the agenda today is a committee update with respect to the GSK, Lyme disease vaccine, LYMErix, followed by an open public hearing in which we are aware of nine individuals or organizations that wish to be represented there.

In the interest of expediting the sequence and allowing everyone to be heard, I'd like to ask the nine individuals, who are on our agenda as scheduled to speak, to come down into this area on the side, if they would, so that they can come up to the microphone at the time we announce them.

They are currently Karen Vanderhoof-Forschner, Norman Latov -- I hope that I'm not butchering anyone's name. I

apologize if I am -- Mark Geier, David Geier, Stephen Sheller, Lonnie Skall -- Lonnie Skall has canceled -- Kathy Shepanski, Pat Smith, and Jenny Marra.

So thank you very much to those individuals for accommodating us.

I would like to now call on Patricia Rohan, who is already at the microphone -- thank you -- for a committee update on the GSK Lyme disease vaccine.

Dr. Rohan.

DR. ROHAN: Good afternoon and as Dr. Daum mentioned, I would like to briefly update the committee on the status of LYMErix, Lyme disease vaccine. You may be aware that LYMErix was voluntarily withdrawn from sale earlier this year. The sponsor, GlaxoSmithKline, halted distribution and made their announcement in February 2002, citing poor sales as the reason for this decision.

GlaxoSmithKline further recommended that no additional vaccinations be administered, particularly for those considering initiation of the three-dose vaccination series.

Clinical trial vaccination was ended. The information was disseminated in a series of letters to doctors, to investigators, and to distributors. There was a mechanism provided for refund for returned vaccine.

I'd like to turn now, for a moment, to update you on the status of the Phase IV safety study for LYMErix. This is

based on an interim report, not an interim analysis.

As you may recall, may or may not recall, the overall goal was to detect rare, but significant adverse events that are associated with product use that may not be recognized in studies of the sizes typical for pre-licensure studies.

In the original plan, there were 25,000 adults who would be aged and gender matched to 75,000 unexposed controls accrued over a two year period at the Harvard Pilgrim Health Care HMO.

Events are identified using ICD-9 billing codes and include both ambulatory and in-patient claims data.

Outcomes are confirmed by blinded review. Record review is completed by the appropriate sub-specialist and established diagnostic criteria are used where applicable.

The incidence of predefined adverse events in the exposed cohort are compared to the incidence in the unexposed cohort.

The primary endpoint for the study is new onset inflammatory arthropathy, and other endpoints include selected neurologic disorders, Lyme disease, rheumatoid arthritis, allergic events, hospitalization, and death.

Due to low accrual rate, additional HMO sites were added late in 2001. These include the Tufts HMO System in New England and Health Partners located in the upper Midwest.

In addition, the accrual period was extended to

three years.

This is a recap of the accrual at various time points. The initial planned accrual of 25,000 vaccinees. After nearly two years, 2,568 vaccinees, just a little over ten percent of what had been anticipated, and with the additional activities that I have just mentioned, there are now 7,643 vaccinees with unexposed matched controls.

This is a breakdown of those 7,643 vaccinees and their controls by site. So you can see that the Harvard Pilgrim Health Care System has continued to accrue over a thousand subjects in a little over the last year, year-and-a-half. The Tufts System and Health Partners are each now contributing close to 2,000 vaccinees.

Now for those subjects accrued to date, we have the ICD-9 codes, the events that have occurred since the time of their first LYMErix vaccine onward. There are 847 musculoskeletal events that have been reported in the vaccinees and 2,063 in the unexposed.

There are various levels of review that these events then go through. The first level by registered nurse takes out many events, primarily trauma and injury, which is the bulk of musculoskeletal events, and then goes to a second level of review by a rheumatology fellow.

After that level, possible inflammatory arthropathy is then sent on to a rheumatologist, who uses an

adjudication form to determine new onset inflammatory arthropathy.

As you can see, there are seven new onset inflammatory arthropathy cases in vaccinees and 15 in the unexposed as of the eighth quarterly report, which was submitted to us early this year.

I also wanted to point out that the other numbers that you see on the table, except for the bottom row, these are events not people. The bottom row is how many people with those events. So it is hard to make a direct comparison at this point.

In conclusion, GlaxoSmithKline has committed to full safety follow-up for all ongoing adults and pediatric clinical trials. They will also complete the Phase IV post-marketing study with full four year post-vaccination follow-up. That is slated to be completed in the year 2006.

In the meantime, we will continue to monitor IND and VAERS reports for safety issues.

Thank you for your attention.

CHAIRMAN DAUM: Thank you.

Are there committee questions for Dr. Rohan? Clarification issues?

(No response.)

CHAIRMAN DAUM: Dr. Rohan, we thank you very kindly.

We will now turn to the open public hearing portion of this session. There are now, as I understand things, eight individuals who have requested time to speak. I'd like to ask them each to limit their comments to five minutes. We will time them and provide input for you by this little traffic light device sitting on top of the projector which will turn green when you start, orange after you have spoken for four minutes, and red after you have spoken for five minutes.

And I thank you very much for cooperating. We look forward to hearing your comments. In advance, collectively, we thank you very much for taking the time to come today.

Ms. Karen Vanderhoof-Forschner. I hope I'm pronouncing your name correctly.

MS. KAREN VANDERHOOF-FORSCHNER: Yes, that's fine.

CHAIRMAN DAUM: I apologize if I'm not.

MS. KAREN VANDERHOOF-FORSCHNER: Thank you.

Okay. I'm Karen Vanderhoof-Forschner, President and Chairman of the Board of Directors of the Lyme Disease Foundation, or LDF, established in 1988.

The LDF is the only nonprofit meeting federal standards as a national nonprofit. We represent millions of people across the country and have a database of 85,000 supporters, that includes family researchers, business people, and government employees.

We have held 16 international scientific

conferences; have state and federal public policy programs; coordinate a network of task forces and support groups; and have funded research programs that resulted in a 130 publications.

All members of my family, including my pets, are fully current in our vaccinations. Every year, I voluntarily take the flu vaccine and I have recently taken the pneumonia vaccine.

I am keenly aware that this committee takes seriously its duty to weigh the risks and benefits of each vaccine based on scientific data and the public need.

Today I am here in a continuing role to keep you informed of additional science relating to the safety and efficacy of the Lyme vaccine. I have given you a packet today, like this one, because I have no doubt that you will see the LYMErix vaccine back in the marketplace with the current or a different manufacturer for adults and pediatrics.

In this packet you will see, on the top, a patent for a safer Lyme vaccine. This is the United States version of the safer vaccine as compared to the current OspA vaccine filed in March of 2000, ten months before this committee held its special Lyme disease vaccines last January.

I have discussed these patents with the Advisory Committee members who felt that their recommendations would have been significantly different if they were aware of this and other material that I had given your committee last November.

Also in this packet is a 1997 memo to the Lyme Disease Foundation from SmithKline Beecham guaranteeing us that anyone who tested positive for Lyme disease would be excluded from the trial, and nobody would be included in the trial unless they had had their test run beforehand. This was not true at that time according to FDA documents and corporate documents.

Why will the public and scientists not necessarily believe the VAERS data that has been presented here today? Probably because science indicating opposite scientific conclusions are not presented at the same time or at other governmental forums, yet have been presented.

Because of the personnel from the CDC, which is Ned Hayes and Dave Dennis, have a perceived conflict of interest because they sat on SmithKline Beecham's private data safety monitoring committee and were at the same time in charge of the CDC's working advisory committee, working group on the ACIP's recommendations for use of the vaccine, people will wonder if this data is tainted.

Indeed, in this packet, you will notice five of the nine people on the ACIP working group had conflicts of interest.

One was an employee of one of the Lyme disease vaccine manufacturers, and the other was a private consultant to a second Lyme vaccine manufacturer.

And at least one of the CDC individuals in this

that was a consultant to SmithKline Beecham was also involved in the VAERS analysis, leading to a public perception of a conflict of interest.

After my presentation, you will hear Lyme disease adverse event data from the LYMErix vaccine by Dr. Mark Geier, a world renowned VAERS data analysis expert. He will be followed by Dr. Norman Latov, a world renowned expert in peripheral neuropathy from Cornell, New York. And then, David Geier, regarding VAERS data analysis.

At a future date, we will be here to present research that directly questions the validity of the Western blot data used to determine which vaccinees did or did not get protection from the Lyme vaccine.

Thank you very much.

CHAIRMAN DAUM: Thank you very much, Ms. Vanderhoof-Forschner.

I show next Dr. Norman Latov; is that correct sequence? Okay.

Thank you, Dr. Latov, and welcome.

DR. LATOV: I'd like to bring to the committee's attention the occurrence of neurological sequelae following Lyme vaccination.

In the past several months, we have seen several patient who developed neurological impairment after the vaccine. Four patients had a demyelinating peripheral neuropathy

documented by EMG and nerve conduction studies. Three had cognitive impairment with leukoencephalopathy and multiple white matter lesions in their MRI's. One had both neuropathy and leukoencephalopathy.

The syndromes are strikingly similar to those seen in patients with chronic Lyme disease who have had active infection in the past and treated.

In most of the patients the symptoms were presumed to be due to arthritis. Prior to a neurological evaluation the correct diagnosis was initially missed. So I think there are more patients such as these, but they really have not been evaluated properly.

By sequence analysis, the OspA protein in the LYMErix vaccine has three regions of homology, each consisting of six amino acids corresponding to brain cDNA sequences in the GENBANK database.

In addition, a human genomic database search revealed 16 additional regions of homology of six amino acids or more corresponding to genomic sequences. The observation suggests that the LYMErix vaccine may have induced an autoimmune reaction to a cross-reactive neural protein in the central or peripheral nervous system, resulting in neurological disease.

A similar autoimmune reactivity induced by infection might be responsible, in part, for the neurological manifestation of chronic Lyme disease.

Patients administered the LYMErix vaccine and their physicians need to be informed as to the possible development of neurological sequelae and be properly evaluated if the symptoms are present. It would also be important to examine patients vaccinated with the vaccine, who develop neurological disease, to determine whether they have T or B cell reactivity to the cross-reactive epitopes.

In addition, there is a need for studies to determine how to best treat these patients as they might have both an autoimmune disease and ongoing infection in some cases.

Thank you.

CHAIRMAN DAUM: Thank you very much, Dr. Latov.

DR. KATZ: Could we have a question?

CHAIRMAN DAUM: We don't usually do that, but we have time for one quick question sure.

DR. KATZ: Can you tell us did these patients developed their symptoms after the second dose, the third dose, or how long afterwards? Can you give us any time sequences at all?

DR. LATOV: Three of the patients developed symptoms acutely after the third vaccine which is a year after the first, with a severe flu-like syndrome, followed by weakness, paraesthesia, et cetera.

A couple developed after the second dose, never received a third dose. One patient started noticing mild

symptoms after the first dose and then progressed thereafter.

So it is variable, but the ones with the most striking onset were after the third dose.

DR. SAMUEL KATZ: Thank you, very much.

DR. LATOV: Yeah.

CHAIRMAN DAUM: Thank you, Dr. Latov.

Dr. Mark Geier. Again I hope I am saying names correctly.

DR. MARK GEIER: I'm Dr. Mark Geier of the Genetic Centers of America.

I have spent the last 15 or 20 years working on adverse events in vaccines, and I would like to present a little data from a paper that we have recently had accepted for publication in a peer-reviewed journal.

Basically, we studied in the VAERS database. We compared the adverse reactions to those receiving TD vaccine, which is a vaccine that has been found to be causally associated with peripheral neuropathies by the National Academy of Sciences. And we also compared adverse reactions to LYMErix with the MMR vaccine, with the Rubella vaccine having been found, again by the National Academy of Sciences, to cause acute and chronic arthritis.

Next slide, please.

We did this to control for various things that need to be controlled for in the study of the VAERS. We found

that when you compared TD vaccine to Lyme vaccine, there was a tremendously significant, and clinically significant, increase in the rate of total reactions, ER visits, life threatening reactions, hospitalizations, and disabilities, and an increase in death, but it wasn't large enough to be statistically significant.

Next slide.

When we looked at the severe adverse reactions comparing with TD and LYMErix, we found that there was a statistical increase in arthritis; chronic arthritis as defined by arthritis still around one year later since VAERS follows up at a year; neuropathy, chronic neuropathy; convulsions which were not significant; thrombocytopenia; lymphadenopathy; hair loss; and the whole list that is up here. Because of time, I will just show it you.

But basically, arthritis and neurological disorders were clearly compared to a vaccine that everybody admits causes some neurological disorders.

When we compared LYMErix to the rubella vaccine, looking specifically at arthritis, both chronic and acute, we found a very large increase of arthritis of both kinds compared to the rubella. And remember, rubella is a vaccine that again is widely accepted as causing in itself chronic and permanent arthritis.

So we found that it is very remarkable that this

vaccine caused significantly more than a vaccine that we know causes arthritis.

We looked at a paper, this paper that is listed here. These authors looked at and found similar numbers to what we found, but they concluded that the LYMErix was generally well tolerated and that there were no, or very few, unexpected reactions. It all depends on what you expect.

I mean, here is a vaccine that causes tremendously higher rates of neurological reactions and chronic and acute arthritis than vaccines that are admitted to cause those things. And yet these were considered to be generally well tolerated.

Our data and our analysis of our data does not show them to be well tolerated at all, but rather very poorly tolerated.

The question to ask is how could they find that they were generally well-tolerated. I think that is just a point of view. I mean, they didn't cause anything that hadn't been seen in the studies, I guess.

But I think that our recommendation for current LYMErix vaccine is that either it shouldn't be reintroduced or if it is reintroduced it should be recommended only in cases where there is a very high rate of Lyme in the area and then only with informed consent. That is, the patients and the doctors have to be aware that there are high rates of adverse reactions, some of them very severe.

In addition, they have to be aware that there is treatment for Lyme. Lyme, although it is a bad disease, responds very well to antibiotics if they are given in a timely fashion and given in the correct amounts.

Our better recommendation is that we wait and introduce a better vaccine that doesn't have so many adverse reactions.

As a final statement, I would like to point out that I am strongly pro-vaccine. I just am interested in the improvement and in full disclosure of vaccine problems.

Thank you.

CHAIRMAN DAUM: We thank you.

David Geier, is our next speaker.

MR. DAVID GEIER: My name is David Geier and I'm President of Medcon, which is a company that analyzes adverse reactions to vaccines.

I don't have a conflict of interest in this.

What I am going to present to you briefly here is about epidemiology of the Vaccine Adverse Event Reporting System, or VAERS database. This is in light of what my dad just presented before.

As what you know, CDC has maintained VAERS since 1990. Adverse reactions are required to be reported to this database as commanded by U.S. law despite claims by other people.

Additionally, the CDC requires written telephonic communication of these reactions. The CDC additionally follows up these reactions to determine whether patients recovered from their reactions or not.

This is what we classify as chronic reaction, those patients who haven't recovered at one year following vaccination from their adverse reaction.

Additionally, the VAERS working group analyzes and publishes epidemiological studies based on VAERS. And Mark Geier and myself have published more than 20 articles in peer-reviewed medical journals analyzing VAERS for the types of adverse reactions he described following Lyme vaccine.

Additionally, VAERS working group reported how useful VAERS is.

Next slide.

VAERS database includes important information. It is listed up there. Of particular interests are the co-starts. These list the adverse reactions that were reported following vaccinations.

Additionally, it gives information about which vaccine was attributed to the adverse reaction that was reported and what year.

What we have done that is new is that we have used Microsoft Access, a relational database, to assemble the whole VAERS so we can analyze it at one time with one search. So we

can analyze any of the fields that are found in VAERS.

Additionally, we used biological surveillance summaries compiled by the CDC to calculated the incidence rates of adverse reactions.

When doing that the question arises what does that mean because VAERS is complicated by under-reporting and erroneous reporting. So we have used vaccine control groups in order to alleviate this.

A vaccine control group is a vaccine administered to a similar age population as the vaccine under study.

So our hypothesis is that an unbiased search of VAERS database should yield non-statistically significant differences in the incident rates of adverse reactions administered to a similar age population because the inherent limitations in VAERS should apply equally to both vaccines as well as the biological surveillance summaries. Their limitations should apply equally to each vaccine.

Some of the terms that you saw in the slides previously presented on VAERS: we use relative risk. That is the vaccine under study by the control vaccine.

Trivial risk is just subtracting one from the relative risk.

Percent association is dividing the relative risk by the relative risk plus one.

The overall importance of these statistical kind

of calculations is that we believe that if you have an adverse reaction, following a vaccine, in comparison to a control group with the percent association greater than or equal to 67 percent or relative risk greater than or equal to two or trivial risk greater than or equal to one, and that additionally these criteria are listed, that it's medically plausible for a component of the vaccine to cause the injury alleged; that the association between the vaccine and the alleged injuries was reported in the peer-reviewed literature; and the vaccinee suffered an injury which is medically accepted as a possible reaction; and that the injury occurred within a medically accepted time period; and the alternate causes were considered but otherwise limited; then more likely than not you can say the vaccine caused the alleged injury.

And as with the case with Lyme, we believe that each of these criteria has now been met.

Thanks.

CHAIRMAN DAUM: Well, thank you very much.

Stephen Sheller, please.

MR. BROOKS: Thank you, my name is Albert Brooks. I'm an associate of Mr. Sheller. Mr. Sheller has become unavailable and asked me to appear in his stead.

Chairman Daum, members of the committee, I want to thank you for the opportunity to speak here today.

I must express a bit of puzzlement at why we're

here. It is so late in the afternoon at this time and this place given no questions being posed to the Advisory Committee and given the FDA's presentation.

But I do want to echo what has been said earlier and point out that this vaccine, from what I can see -- and we have been contacted. We are attorneys in Philadelphia -- we have been contacted by well over 500 people now who have experienced arthritis, general Lyme disease-like symptoms, and very, very serious neurological conditions, such as those described by Dr. Latov, including one patient with acute transverse myelitis who is now on a trach tube and a feeding tube and will in all likelihood be dead soon after vaccination with LYMErix, and that occurred within a week of her second vaccination.

This vaccine is really a cautionary tale about what happens when qualified recommendations for approval are made.

In 1998, there were a number of safety concerns that were expressed by the committee, albeit with a recommendation for approval.

In January of 2001, many of those concerns were revisited and the committee stated, by and large, that many of those safety questions had not yet been resolved, given two years of marketing.

The committee did make several recommendations about what should be done, many involving the dissemination of

information to the public and to doctors about the ongoing safety questions.

In that past year, as far as I can tell, none of that has been done. Information has still not gotten to the public. And there is more information that has come out since then.

We have the information from Dr. Latov. We have the development in the VAERS reporting system. And we also know that the FDA is looking at the VAERS Reports, albeit in a very limited way, specifically with arthritis.

They have, as of November when they presented an abstract to the Rheumatology Convention, gathered records on 31 people who had full sets of records and arthritis complaints. Fourteen of those had physician-diagnosed onset of arthritis and that is a very strict definition.

Seven of those 14 could not otherwise be explained by preexisting conditions, family history, predisposition to autoimmune-related conditions and these are of quite a bit of concern to us.

Most importantly we have the vaccine being withdrawn from the market, suddenly, and at the very beginning of what is believed to be the tick season in most of the Lyme endemic areas, which raises substantial questions about the safety profile of this vaccine.

I think it is strains credibility for the

manufacturer to maintain that it is being withdrawn because of poor sales due to lack of demand, especially in light of the CDC's recent analysis that the incidence of Lyme disease is higher than ever.

The reason there are poor sales -- and I think that poor uptake into the Phase IV study demonstrates that there have been poor sales -- is because this vaccine is not a good vaccine and it is hurting people.

And many people are reporting adverse reactions. The numbers reported to VAERS are remarkable, and they are only the tip of the iceberg.

I have talked to people who have gone for months after vaccination not realizing that arthritis is possibly related. Therefore, they never associated their arthritis with the vaccine.

I have talked to people who have said they are 40 and they feel like they are going on 80. People who say they felt like they were just getting old; that's a 35 year-old. I have talked to a client, who was a vice president of a major manufacturing company of clothing, a multi-million dollar salary per year, who is no longer able to work; would hold meetings in the afternoon and the next morning forget that the meetings occurred. She has now a lupus-like condition. I have talked to several people like that.

It is not enough for the vaccine to have been

voluntarily withdrawn and the Phase IV study is not enough. We are calling on the FDA to actively solicit information from doctors and the public regarding arthritis and the more generalized Lyme disease conditions, as well as neurological symptoms, to really build a meaningful database.

It's not acceptable that this vaccine can come on the market for two years, be withdrawn, and leave injured people in its wake with really no answers.

The public health demands an answer. People who have been injured demand an answer. The treatment of people who have been injured and the treating physician's ability to treat those people demand an answer.

That is what we are requesting at this point. And we certainly hope that the disappearance of the vaccine from the market will not also bring with it a disappearance of an investigation of these conditions.

Thank you.

CHAIRMAN DAUM: Thank you very much.

Kathy Shepanski.

MS. SHEPANSKI: I'm Kathy Shepanski and I am a LYMErix victim. I received --

CHAIRMAN DAUM: Ms. Shepanski, excuse me. Can you speak right into the mic?

MS. KATHY SHEPANKSI: Oh, I'm sorry.

CHAIRMAN DAUM: Thank you. We want to be able to

hear you.

MS. KATHY SHEPANSKI: All right. I'm a LYMErix victim. I received one shot in May of 1999, May 4th. By May 6, I was starting to feel like I had the flu and that was the only reaction that anyone told me that I would get.

I became very ill. I did not receive the second shot because they were deciding whether they were going to put me in the hospital on the day of my second shot.

I have been to many doctors that they don't even want to hear what you have to say.

Finally, I have gotten to a doctor that has diagnosed me with Epstein-Barr and rheumatoid arthritis. That's where I am.

I was perfectly healthy before LYMErix shot and now I'm not.

Thank you.

CHAIRMAN DAUM: Thank you very much, Ms. Shepanski. We hope you recover as quickly as possible.

Is Pat Smith here, please?

MS. SMITH: Thank you, Mr. Chairman and members of the committee.

My name is Pat Smith. I'm President of the Lyme Disease Association, an all volunteer association with five nationwide affiliates. It consists of patients and families of patients.

The LDA has provided funding for research from coast to coast, some published in peer-reviewed journals including JAMA.

Along with our Greenwich affiliate, we were recently honored at a luncheon by Columbia University for partnering with them in the establishment of an endowed chronic Lyme disease research center at Columbia.

We also co-sponsored a fully accredited medical conference for physicians with Columbia.

Working with legislators, we have developed a bill in Congress, H.R. 1254, which will provide $125 million for Lyme disease research, prevention, and physician education.

The association provided testimony to this committee in January of 2001 seeking a moratorium on the vaccine, but we felt that no action was taken by the FDA. And to that end, in January 2002, the LDA had a private meeting with the FDA's Center for Biologics Evaluation and Research, CBER. We brought along several experts to discuss the vaccine issue with FDA officials, including Karen Midthun, Susan Ellenberg, Peter Beckerman, Norman Baylor, Miles Braun, and Robert Ball.

It is my understanding that the committee has not received an update on that meeting, and I would like to present a quick update.

We presented Dr. Donald Marks, M.D., Ph.D., former Lab Director of Connaught, 14 years of clinical research and

regulatory affairs experience in the pharmaceutical industry, including Director of Clinical Research in charge of the Lyme disease vaccine program at Aventis Pasteur; presented to the FDA and he was the leader of a competitive effort to manufacture a virtually identical vaccine.

Currently, his focus is diagnosis of adverse events from medications, vaccines, biologicals and medical devices. The LYMErix associated cases he reviewed included: arthralgias and arthritis, as well as complicated neurological problems, and include adverse events that are long lasting.

A summary of Dr. Marks' presentation follows.

Why more adverse events were seen after the vaccine reached the market? People receiving LYMErix after product launch lived in Lyme endemic areas. Many people may have had prior exposure and clinical or subclinical infection. In these cases, LYMErix could be triggering or reactivating the damage caused by old and presumably cured Lyme disease.

Pattern of symptoms experienced after LYMErix mimic patterns of prior infections in many individuals. In these patients, LYMErix-related symptoms seem to respond to antibiotics as did the initial infection, bolstering the theory of disease reactivation.

Issues which confuse the vaccine picture. As proof of safety, the company inoculated arthritis-prone mice with OspA. But since the mice did not possess the HLA marker known to

interact with OspA in humans, this rendered the experiment meaningless.

The company masked serious causally-related adverse events behind qualifiers, such as, quote, and which may have no causal relationship with the vaccine, unquote, and, quote, cannot be distinguished from the natural history of the underlying disease, unquote.

The company says that the possibility of severe rheumatological neurologic autoimmune adverse events is inherent in Lyme disease, attempting to shift the blame onto the patient and their illness, but does not inform physicians that the same adverse events can be separately caused by the vaccine, in addition to the symptoms of an underlying disease.

As a result of these actions, general practitioners in the U.S. were kept in the dark about the life-threatening side effects of LYMErix. Some basic problems: non-specific hyperactivation of the immune system, often evidenced through swollen hands or arthritis is an adverse event associated with LYMErix. This may be due to the presence of adjuvant.

This hyperactivation creates "dirty" Western blots in which multiple Lyme disease bands appear whether the individual has Lyme disease or not. The dirty banding makes it impossible for physicians to differentiate between LYMErix vaccination, new infection, or reactivation.

The net result is that cases of Lyme disease will

go undiagnosed and untreated. Adverse reactions to LYMErix will be misdiagnosed as Lyme disease and people will be unnecessarily treated with antibiotics.

The vaccine manufacturer provides no warning to these possibilities.

The intention of FDA regulations is to provide a vaccine that is safe and effective. The intention of prescribing regulations is to provide sufficient information to prescribing physicians to enable safe and effective use of the vaccine. In both regards, SKB's actions appear to be contrary to FDA regulation and intentions and contrary to accepted standards within the vaccine industry.

The cases he examined, four of four neurologicals that he felt were related; 15 of seven rheumatologicals.

And just in conclusion, I would just say that I do have a copy of the remainder of my talk and I would ask that the committee does not drop this. We do not want this vaccine to be re-marketed or a similar vaccine without studies being finished.

Thank you.

CHAIRMAN DAUM: Thank you very much, Ms. Marra or Ms. Smith. Excuse me. I get confused.

Ms. Marra is the next and last scheduled speaker. Ms. Marra.

MS. JENNY MARRA: My name is Jenny Marra and I'm a Hospice nurse from New Jersey and I am a vaccine victim.

Some may remember me from January 31st meeting of 2001. I was here with a lot of different people that I have met that were also hurt by this vaccine.

I don't have the gumption; I don't have the health that I had then.

I want to put a face on these numbers that you are looking at. My life has been destroyed, completely. I have an elbow as big as a knee.

The symptoms came on a week after the first injection. The doctors, I have seen 17 of them. Three know about LYMErix and the problems it is causing. The others don't.

I have been diagnosed with fibromyalgia and depression. My husband is the same way. We both have fibromyalgia and depression at the same time. According to him, this is possible.

I don't understand. I am hearing from the VAERS investigation. I did the telephone investigation from the FDA. I don't understand the numbers, that they're not finding a connection.

When I know personally 133 people that have had this vaccine and that are hurt and out of them 121 of them are just like me, and we can't get help.

So if you can't find this connection, we're never going to have doctors to be able to find -- I'm not even looking

for a cure. I just want treatment. I need -- I need help. I am in pain and I need help.

And I want to know if you people care. Do you?

You are the FDA. At times you could trust what you put on the market. I tell you what. I wouldn't touch anything that you put on the market anymore, not from what I've learned since taking this vaccine.

And I'm a nurse. I'm a nurse. I'm 43 years old and I'm going on 80 and I'm not alone. There's thousands of people just like me. Why can't you find the connection? I don't understand.

I'm not allowed to ask questions, am I?

CHAIRMAN DAUM: You're welcome to ask them. And we'll --

MS. JENNY MARRA: Can you answer me?

CHAIRMAN DAUM: I don't know.

MS. JENNY MARRA: Yeah, I did not think so.

I am in touch with several people in the FDA that are -- you have non-medical people doing these investigations on the phone. Have you once physically examined any of us?

We have doctors. They have no idea what's going on with us. All of us. I mean, I know 121 people just like me, with the same symptoms, the same problems.

You know, I have memory loss. I can't even use my right hand right now because I drove here yesterday from New

Jersey. You know, there's so many people like me. You can't, you know, you can't -- for one, I keep hearing people talk about them putting it back on the market, God forbid. You know, enough people have been hurt.

I also heard that SmithKline is following up on the people that were in the studies. I know 11 people that were in those studies and they have been trying and trying to get SmithKline to help them, as they promised, and they are doing nothing. They are shutting them out. They are shutting the doors. It's over. It's over.

I just ask -- you know, I don't even know what I'm asking, except for help. I need help. I can't live on steroids. It is the only thing that does give us some relief when it flares up.

But I can barely walk mornings. Today I'm lucky. I only have loss use in my hand. Half the time it's my arms. I have memory loss. My husband is worse than I am. And I have a son that I can't play with anymore.

CHAIRMAN DAUM: Thank you, Ms. Marra, for sharing your touching story with us. We wish you a speedy recovery, as well.

I think we want to reassure you that the committee remains concerned about the safety and the efficacy of all the vaccines we discuss here and will continue to do so.

Is there anyone else that would like to address

the committee at this time as part of the open public hearing?

(No response.)

CHAIRMAN DAUM: Ms. Fisher, did you want to make a comment before we close?

MS. FISHER: Yes. I had wanted to ask a question to the FDA, but didn't get my hand up in time when you were looking around.

I just, you know, I think it is very important for us to take seriously patterns. And that's what Ms. Marra was trying to communicate. We see this often.

Certainly at the National Vaccine Information Center, we see many patterns with the reactions that are being reported. I certainly hope that we will follow up on those patterns.

But I would like to ask the FDA: now that LYMErix has been voluntarily withdrawn from the market by the manufacturer, what is the process for LYMErix to be reintroduced in the U.S.?

Specifically, can this vaccine be reintroduced and used in children, without supporting data first being presented to this committee for a vote on safety and efficacy?

CHAIRMAN DAUM: Okay. Thank you.

Let's ask someone from the agency to respond.

Thank you, Dr. Midthun.

DR. MIDTHUN: This vaccine has never had an

indication for a pediatric use, and so if that scenario were to ensue, clearly that indication would have to be sought.

As you know, we routinely bring these types of things to the Advisory Committee for your input.

CHAIRMAN DAUM: Thank you, Dr. Midthun.

And again thanks to the people who took the time, and effort, and energy to come to address up today. We assure you we will take your comments seriously and under advisement.

With that, I declare the meeting adjourned.

(Whereupon, at 3:35 p.m., the meeting was concluded.)