UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE MEETING

TUESDAY,

MAY 21, 2002

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The Advisory Committee meet in the Maryland Room, Silver Spring Hilton, 8727 Colesville Road, Silver Spring, Maryland, at 8:30 a.m., Dr. Robert S. Daum, Chairman, presiding.

PRESENT:

ROBERT S. DAUM, M.D., Chairman
MICHAEL DECKER, M.D., M.P.H., Industry Representative

PAMELA S. DIAZ, M.D., Member

WALTER L. FAGGETT, M.D., Member

BARBARA LOE FISHER, Community Representative

MIMI GLODE, M.D., Consultant

JUDITH D. GOLDBERG, Sc.D., Member

PRESENT (Continued):

HOLLI HAMILTON, M.D., M.P.H., Consultant

SAMUEL L. KATZ, M.D., Member

DAVID M. MARKOWITZ, M.D., Member

GARY D. OVERTURF, M.D., Member

JULIE PARSONNET, M.D., Member

RICHARD H. SCHWARTZ, M.D., Consultant

DIXIE SNIDER, JR., M.D., Consultant

DAVID S. STEPHENS, M.D., Member

RICHARD J. WHITLEY, M.D., Member

JODY SACHS, D.P.M., Executive Secretary

C O N T E N T S

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

(8:34 a.m.)

CHAIRMAN DAUM: Good morning and welcome. I would like to begin by asking committee members, old and new, and temporary voting members, all those people at the table really, to introduce themselves.

Dave, if you're up for it, we'll start up at your end, please.

DR. STEPHEN: David Stephens, Emory University and other places in Atlanta.

DR. KATZ: Sam Katz from Duke University.

DR. HAMILTON: Holli Hamilton, DMID, NIH.

DR. GLODE: Mimi Glode, pediatric infectious disease, University of Colorado.

DR. OVERTURF: Gary Overturf, University of New Mexico.

DR. FAGGETT: Walt Faggett, D.C. Department of Health, Private Practice Pediatrics, Washington, D.C.

DR. GRIFFIN: Diane Griffin, Johns Hopkins School of Public Health.

DR. WHITLEY: Rich Whitley, University of Alabama at Birmingham.

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

DR. GOLDBERG: Judy Goldberg, New York University

School of Medicine.

DR. MARKOVITZ: David Markovitz, University of Michigan.

DR. PARSONNET: Julie Parsonnet, Stanford University.

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

DR. KOU: Jingyee Kou, FDA.

DR. PRATT: Douglas Pratt, FDA, Office of Vaccines.

DR. GOLDENTHAL: Karen Goldenthal, FDA.

CHAIRMAN DAUM: I'm Robert Daum from the University of Chicago.

DR. SACHS: And I'm Jody Sachs with the FDA, the Executive Secretary for VRBPAC.

CHAIRMAN DAUM: There are a number of people at the table for whom this is their first meeting, including, of course, Dr. Sachs, who has taken over the Executive Secretary role from Nancy Cherry. Tough shoes to fill, but Dr. Sachs is up to the task and I have no doubt will be steering us through with the same aplomb as Nancy Cherry used to do.

In fact, we'll now turn the floor over to her, please, for a conflict of interest statement.

DR. SACHS: Thank you.

I want to welcome everybody, and I'd like to read

the conflict of interest statement for the record.

The following announcement addresses conflict of interest issues associated with the Vaccine and Related Biological Products Advisory Committee meeting on May 21st, 2002. The Director of the Center for Biologics Evaluation and Research has appointed Dr. Mimi Glode, Holli Hamilton, and Dixie Snider as temporary voting members for the discussions during this meeting.

In addition, the Senior Associate Commission for Communications and Constituent Relations has appointed Dr. Richard Schwartz as temporary voting member.

To determine if any conflicts of interest exist, the agency reviewed the submitted agenda and all financial interests reported by the meeting participants. As a result of this review and based on the FDA draft guidance on disclosure of conflict of interest for special government employees participating in an FDA product specific advisory committee meeting, the following disclosures are being made.

Dr. Richard Schwartz has been granted a waiver under 18 USC 208(b)(3) and under 21 USC 355(n)(4), Section 505 of the Food and Drug Administration Modernization Act for stock in competing firm valued you at $5,001 to 25,000. Dr. Schwartz may participate fully in the discussions of the safety and efficacy of Prevnar for acute otitis media indication.

We would like to note for the record that Dr. Michael Decker is participating in this meeting as an industry

representative acting on behalf of regulated industry. Dr. Decker's appointment is not subject to 18 USC 208. Dr. Decker is employed by Aventis.

In the event that the discussions involved specific products or firms not on the agenda and for which the FDA's participants have a financial interest, the participants rare reminded of the need to exclude themselves from the discussions. Their recusal will be noted for the public record.

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

A copy of the waiver addressed in this announcement is available by written request under the Freedom of Information Act.

And I also would like to ask as a courtesy to the committee discussion and your neighbors in the audience please put your cell phones and pagers on silent mode. If you need to use your cell phone, please step out in the hall.

And with that, I'd like to turn over the meeting to our Chair, Dr. Daum.

Thank you.

CHAIRMAN DAUM: And those that have just turned their cell phones and pagers off, we thank you.

I think we'll try and zip right along here and

turn to business at hand. The first item for discussion today is an open session. We are discussing the role of Prevnar for an acute otitis media indication.

And we will begin with a two-part, as I understand it, sponsor's presentation, beginning first with Steve Black, which will give us a Prevnar update.

Welcome, Dr. Black.

DR. BLACK: Good morning. I've been asked to give an update on an ongoing post marketing, Phase IV study that we're conducting within Northern California, Kaiser Permanente, of the Prevnar vaccine, and I'll give you an update which includes an interim analysis on safety and results regarding the changes in epidemiology that we have observed of pneumococcal disease in our population.

The post marketing study that I'm going to describe to you, let me give you a little bit of background on that. The vaccine Prevnar was licenses in February of 2000, as you know, and post marketing surveillance began in our population very shortly thereafter with general availability of the vaccine in April.

And the vaccine is being given now routinely to children concomitantly with other vaccines.

What I'm going to describe to you this morning in terms of safety is a second interim look on data through December 31st, 2001. There was an earlier interim look through December

of the year prior to 2000, which has been submitted to the FDA, and they've had time to review, and this, I should say in fairness to them, has only recently been submitted to them for their review.

Following the review of the safety, I'll talk to you about the impact of the vaccine and present what we think is exciting data on the changes of epidemiology that we've seen, which includes data through the end of the first quarter of this year.

Okay. So this shows you what happens if you keep tinkering with slides, but what I will show you here is that there are two cut points. One is December 2000 and December 2001, and what you can see here is that as of 2000 in the post marketing study or what you can't see -- I'll read it to you -- is that there were about 22,000 first doses given, whereas through December 2001 there were 54,000 first doses given, and there were only 85 fourth doses in the initial look, where there's 17,000 in the second look. So there's substantially more data there.

So back to visible slides now. The way this is set up, and since this is a post marketing study is that there is no control group, and what we're doing is comparing rates of medical utilization within a defined time window, exposure window following vaccine to a control period in the same individuals.

And the exposure window is 30 days for hospital ER

and clinic, and there's an additional window in the clinic of three days that we've used to evaluate possible allergic reactions, for example.

And the control period in these comparisons that I'm going to describe to you is 31 to 60 days following vaccine for all settings.

Also what I'm reporting on here is the subset of children who received the first dose of vaccine at less than 120 days of age. In other words, catch-up and children who started late are not included in this analysis.

And the way we did this is we extracted all diagnoses for medical utilization in the clinic, emergency and hospital, from automated databases that exist at Kaiser Permanente and then rate comparisons were made for all diagnostic categories in the ER and the hospital, and for pre-identified clinic diagnoses as specified in the protocol for the clinic.

In addition, because of concerns expressed regarding a possible association of seizures with receipt of vaccine, we have conducted a review of seizure outcomes using medical record review, and I'll report that separately to you.

To give you an idea, not that you need to read this, this just gives you an idea of the number of diagnoses that were reviewed in the emergency hospital and clinic. These were basically, as I said, for the ER and the hospital all diagnoses, and it's important to be aware of this number because the

statistics that I'm going to be describing to you are not adjusted for multiple comparisons.

And I hope there isn't too much information over here on the right. We'll try to capture that, but what this shows you are the diagnostic categories with elevated risk in this comparison.

This is a hospital setting, an emergency setting, and clinic setting, and then which series: the primary series or the booster dose? And for this analysis the primary series was analyzed as a unit, all three doses together rather than looking at each dose separately.

And what we see here is the outcome and then the rate ratio with a confidence interval and part of the P value here.

And what you can see is really there are two groups of diagnoses. These three, GE reflux, pyloric stenosis, and formula intolerance as a diagnosis.

The rate ratio is here indeterminant because there were no cases in the control group, and then these febrile illness in the emergency room, in the clinic, and fever related diagnoses, which was a predefined diagnostic category in the clinic also showed up, and this entity is basically febrile seizures plus fevers. Febrile illness is pretty much driven by the febrile illness as you can see.

Next slide. Oops, that's me.

Okay. So these are the diagnostic categories with decreased risk. To give you an idea, there are actually more of them than the ones with increased risk, and we really attribute this to the multiplicity of comparisons rather than any protective effect for otitis media, for example, because remember the control period here is in the same children. So that wouldn't really make physiologic sense.

So we looked at these, and the elevated relative risk in a little bit more detail, and this is one of these, febrile illness in the emergency room after the booster dose, and this is the n, the number of events here, and this is the days since vaccination, and the 30-day exposure window.

And what you can see here is what we look for in this type of analysis when we see something that we might think might be physiologic, and that is a clustering of events at one time period, and we see these are eight to ten days following receipt of these vaccines.

If you remember, the booster dose is given concomitantly with MMR in the vast majority of these children, actually more than 90 percent, and we attribute this to the well described fever associated with MMR at this same time interval rather than the fever that we described in telephone interviews where we were actively looking for this and during the trial with Prevnar which was seen earlier on. So we're not really seeing that blip here.

Similarly, in the clinic, we see the same thing with the same time clustering of these events for febrile illness in the clinic and only after the booster dose.

In contrast for GE reflux, what we really see is not that. We see really pretty much a uniform distribution of these events spread out over this time window, and similarly for pyloric stenosis the data is much more sparse, but there really is no time clustering of the event or interpretation either.

Similarly, with formula intolerance as well.

So although seizures did not show up as a positive analysis in these reviews that I showed you, we had planned before doing this interim analysis report to do the seizure review, and let me describe that to you.

What we did is attempted to identify all possible seizure events in automated data by looking for seizure, possible seizure, epilepsy, spasm, shaking or suspicious movements, and those were then reviewed in a manner that was blinded as to whether they were in the exposure window or the control window by trained medical record reviewers using a standardized instrument, and they were classified as definite, probable or possible seizures or the other category was not seizures at all. There was a group of children who were there for maintenance or for assurance or for other things that were really not acute events.

But acute events were classified in one of these categories. Based upon what the physician wrote in the chart, if

they described a definite seizure event or one was described then that was classified as definite, and if the physician's interpretation was that this was a probable seizure, then we took that at face value.

But if it was something that was included as part of a broader differential and they really weren't sure, and there were no confirmatory tests, and no medication was given, we thought it was less likely and that was classified as possible.

So a priori before doing the analysis we had decided we would want the definite and probable seizures together as a group and then analyze them as events, and those were classified as febrile or afebrile based upon, one, whether it's two possible criteria.

One is if it said they were febrile on the chart, we counted it as febrile, or if there was actually fever recorded by one of these two criteria, and our physicians are a little schizophrenic as to which temperature scale they use. So we had both criteria.

And these are the results for seizure, and I'm sorry this is complicated, but if you slide and dice things enough, this is sort of what happens. This is the hospital setting again, the emergency setting, the clinic, and then the series for this comparison, primary and boosters, primary and booster, primary and booster, and then the outcome, afebrile seizures or febrile seizures.

This is the exposed rate. This is the control rate, and then this is the rate ratio with a confidence interval, and then the P value.

To make a long story short, seizures were uncommon in either window and there was no statistical difference for any of these rate ratios. And furthermore, as you can see, there are a fair number that are below one, a fair number that are above one, and there is really not even any suggestion of a pattern here. So we found that quite encouraging in terms of the safety of the vaccine.

And we also looked at, to give you an idea of what these look like, these are emergency visits for febrile seizures after the primary series.

There isn't really any clustering of this, surely not within the first few days where fever is observed with Prevnar.

And after the booster dose, this is not statistically -- there is no statistical clustering here, but we do see that there are more of these events at the same time period where we saw fever in the emergency room as well.

And, again, if there's anything here, we would probably attribute that to the fever of MMR rather than Prevnar.

So a summary of the safety analysis to date, and I would like to emphasize that this is ongoing and not the final results by any means, is that our analysis showed an increased rate of utilization for febrile illness following the booster

dose, and the timing of this fever suggests a relationship to concomitant MMR.

Other events observed with an increased risk, including GE reflux, pyloric stenosis, and formula intolerance, were not felt to be physiologically likely. The analysis, as I said, and data collection are ongoing.

And furthermore, the results are consistent with the first interim analysis which the FDA has had more time to review, as well as with pre-licensure data from our own infancy trial.

So that's the safety data I wanted to share with you, and now I'd like to share some exciting information; at least we think it's exciting vis-a-vis what's happening with disease epidemiology in our population since introduction of the vaccine.

Again, Prevnar was still licensed in February of 2000, and general use began in April. For the evaluation of effectiveness case ascertainment, it's important to emphasize here it was for the whole Kaiser population. One, children and adults, and both vaccinated and non-vaccinated.

So unlike the efficacy trial data we showed you where we're comparing a vaccinated/unvaccinated group, we're really looking here at the population dynamics as a whole and the effectiveness of that vaccine program.

And to look at this effect, we compared the

disease risk in the two years since vaccination compared to prior years, as you'll see. All isolates, Strep. pneumoniae from normally sterile sites were identified from laboratory databases, and then the isolate was sent to Dr. Robert Austrian for serotyping.

The medical records of all the infected children have been reviewed to ascertain and confirm vaccination history and history of any underlying disease.

And then we calculated age specific disease incidence. So this is the graph I would like to show you, and I will remember if we come back next year to move things over to the left here a little bit because we won't be able to see this.

But let me orient you to this slide. This is the incidence in cases per hundred thousand person-years ranging from zero to 120 at the top, and these are years at the bottom. Each dot is a year, and the years are unusual in that they began in the second quarter of each year.

And the reason we did that is that's when the vaccine program began. So we wanted to be able to make the comparison of comparable.

And what we see here in this yellow line is children less than two years of age, and we see that prior to introduction of the vaccine to general use, the disease incidence in this group ranged between 80 and about 110-plus cases per 100,000 person-years and then falls off to virtually nothing

here, less than ten disease incidents during the year beginning in the second quarter of 2001 and ending in the first quarter this year.

Similarly for children under one, the disease incidence as you know is somewhat less, ranging between 50 and almost 100 here and then falls off quite dramatically. You can see this fell off more steeply because that's where the vaccination program began, and for children under five, we see this as well.

There are five cases total that we saw during this year as compared to about 120 during years prior to introduction of vaccine. Only one of those children was vaccinated, and that child was partially vaccinated.

One of the concerns has been that we might see replacement. It's commonly said nature abhors a vacuum, and there's been a concern that other serotypes would come in and causae disease.

I guess I'd better hurry before something happens here. That's okay. I'd rather live with it this way than lose the whole thing.

What that shows in blue is the same graph that I just showed you in the different age groups, and then below these are non-vaccine serotypes, and what you can see is that, one, the incidence is lower as we all know, and if anything, there is a downward slope to the graph although that trend is not

statistically significant, but there's clearly no suggestion of replacement for invasive disease up until this point in time.

And this is something that is actually quite new. This is something that we just presented at the pneumococcal disease meetings in Anchorage a couple of weeks ago, and what we did here is used the same surveillance mechanism to look at disease in older children and adults, and this is the age group here. This is the rate in the five years prior to introduction of vaccine, and this is the rate in the two years after the percent reduction, and part of the P value here.

And what we can see in yellow are shown the two age groups where there's a significant -- or three really if you count this -- age groups where there's a significant reduction in the disease, really quite strikingly dramatic, something we would not have predicted in the 20 to 39 year old age group, a 58 percent reduction in invasive disease in this age group.

Now, most of these have not been serotyped. So this is really all serotype disease. Over age 60 we see a 14 percent reduction, which is also significant, and then over age five we see an 18 percent reduction.

It's important in fairness to say that over age 60 there have been changes in terms of the polysaccharide vaccine coverage in our population which could account for part of this. We estimate there's been about an eight to ten percent increase in coverage over that time period.

But that's not true in this younger age group which we attribute this to the fact that this is the age of the parents of the children who are being vaccinated, and the children it is known -- contact with young children is a risk factor for pneumococcal disease, and we believe that this is entirely suggestive of the fact that herd immunity is operative here and is protecting these individuals.

So, in summary, we've observed a dramatic reduction in basic pneumococcal disease in childhood within our population. The magnitude of the reduction in the first year, which was much greater than the vaccine coverage, and the reduction observed in adults suggests herd immunity effect.

We've not observed any evidence of serotype replacement for invasive disease, and I'd like to say also that Dr. Cindy Whitney of CDC has results from the ABC surveillance program which are consistent with the disease reduction in adults and older children that I've shown you.

Thank you very much.

CHAIRMAN DAUM: Thank you, Dr. Black, for that update.

We have a few minutes for committee questions, if there are, or discussion points. Dr. Katz?

DR. KATZ: Steve, you mentioned the concomitant administration of MMR. Was varicella given at the same time also?

DR. BLACK: Yeah, varicella vaccine, the uptake for varicella vaccine is quite high in our group, and we looked at MMR. There's more than 90 percent of that concomitantly. Usually varicella is given at the same time, but it isn't always. We have not looked at it, but I would guess from past observations we had made it was about 80 percent.

DR. KATZ: The reason I asked is there is some indication that when you give MMR and varicella concomitantly you even further increase the febrile response.

DR. BLACK: At that same interval.

DR. KATZ: Thank you.

DR. BLACK: Actually we'll look at that. that's interesting. Thank you.

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

DR. FAGGETT: Steve, thank you. Those are very exciting reports. A question relative to the experience of Prevnar in the sickle patient. They were probably included under your febrile illnesses, but do you have any information on specifically how the vaccine was tolerated by sickle patients?

DR. BLACK: Yeah, we've not done specific studies on the safety of Prevnar in sickle cell patients. However, the Prevnar vaccine is being routinely used in both younger children with sickle cell disease and in older children as well, and our surveillance does include children with sickle cell disease, and we've not seen during the last two years because they were not

surprisingly targeted for early immunization any cases in children with sickle cell disease.

CHAIRMAN DAUM: Dr. Snider?

Steve, I have one question. The adult data you showed on the last slide are pretty interesting. You mentioned that you haven't yet broken them down by vaccine serotypes and non. Will you be able to do so? Do you have the isolates?

DR. BLACK: No. We started collecting data at the first of this year. We're now -- Dr. Austrian, since the case load in children is reduced, is now willing to do serotyping of adults, and so beginning the first of this year, we're now serotyping all ages, but don't have that historically.

Dr. Whitney at CDC, however, does have serotype data from ABC and I think is analyzing that currently and will be reporting it soon.

CHAIRMAN DAUM: I have on other question. In the very nice curves you showed of what's happened to disease in your area since the vaccine was introduced, you broke down the data between vaccine serotypes and non-vaccine serotypes.

How would that look for the non-vaccine serotypes which did appear to be trending down? If you removed the related vaccine serotypes -- excuse me. The serotypes that are not in the vaccine but are related to those in the vaccine from that analysis.

DR. BLACK: Okay. Let me try and rephrase your

question. What you're looking for are the non-cross-reacting serotypes.

CHAIRMAN DAUM: Right. Thank you for that help.

DR. BLACK: We have a slide for that here. Let me see if I can find it. We also have a million other things.

Oh, you have that somewhere else? Okay. Sorry.

The numbers are smaller and so there's more noise in this, but let me show it to you.

Yeah, okay. So what we have here is, again, the same type of graph, but you'll notice that rather than going up to 120 or 40 here, this only goes up to 20, and again, with the same age groups, under one you can see actually now has a higher incidence of these. Under two, and then under five, and you know, the overall slope here is sort of downward, although I don't understand that, and this dot, this little blip at the end here is really in the same range as these.

So so far, you know, the numbers here are a lot smaller. So it's a little bit harder to interpret, but we don't think this suggests any evidence of replacement disease because the incidence levels here are very low, consistent with what we saw before.

CHAIRMAN DAUM: Thank you.

We'll take two more comments. Dr. Snider, then Dr. Stephens.

DR. SNIDER: Steve, could you tell us what the

serotypes that are vaccine related that you're still seeing are? I mean, specifically people I'm sure that have read the material have some concerns about 19F, for example.

DR. BLACK: Yeah. So the question is, you know, is 19F -- do you mean in vaccinees or in -- yeah, we've really not seen -- I mean the cases of disease that we've seen in the last couple of years since the post marketing took place have not included 19F. There's a couple of fours and one 6B, and that's really about it.

So the concern that we and others had in terms of trying to understand the difference in response to 19F, we're really not seeing that translated into breakthrough disease up until this point in time.

CHAIRMAN DAUM: Dr. Stephens.

DR. STEPHENS: Regarding the effect in young adults, is there any evidence in your health care system of off label use of the conjugate or any increased use of the 23 valent polysaccharide in individuals who may be at risk?

DR. BLACK: Well, we're encouraging increased use in individuals, you know, over age 60. so that has gone up we estimate eight to ten percent over the time period.

The older individuals where we're encouraging its use is primarily hemoglobinopathies or people who are in that category.

There has been some use in older individuals where

it's not indicated, but it's very small. There's four or five individuals for reasons that we can't understand who have obtained the vaccine. Four of them are pediatricians. So maybe that's it. They're enthusiastic and want the same protection for themselves. But they're really a handful. It's very, very small.

So it's not the case in the 20 to 40 year olds. We are going to be undertaking a case control study to look at risk factors and look at this in more detail, but that will take some time.

CHAIRMAN DAUM: Dr. Katz, one last.

DR. KATZ: One quickie. In all of those things that are flashing by when you were trying to find the right slide, one that stood out in my mind was sudden infant death syndrome. That's one that in your primary series you're running through the high risk area.

Can you reassure us about that one?

DR. BLACK: Yeah, let me see if I can find that slide.

DR. KATZ: I don't need a slide. Just tell me.

DR. BLACK: Okay. I mean, the rates that we have for that are not for the last year because the state death tapes lag. So as of the interim report that we did through year 2000, the SIDS rates were about half what the state rate was, and were pretty much identical to what they were in the clinical trial,

which is about .2 per thousand.

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

We sometimes remember and are striving to meet various bars of vaccine safety and various tests and concerns, just how wonderful vaccines are, and it's very gratifying to see this kind of information after the introduction of a new vaccine.

We will move now on to the second part of the sponsor's presentation this morning, which is concerning acute otitis media, or AOM, and we will begin with Dr. George Siber, who will introduce the topic on behalf of the sponsor to us.

Dr. Siber, welcome.

DR. SIBER: Good morning. My name is George Siber. I'm Senior Vice President and Chief Scientific Officer of Wyeth Vaccines.

Is that going to go to right for us? We'll see.

In any event, during the next hour or so we'll present series of presentations on the data and rationale underlying our proposal for an indication for otitis media for the seven valent pneumococcal vaccine, Prevnar.

I'll give a brief introduction on otitis media epidemiology and background. Dr. Terry Kilpi, who is a senior researcher and the head of the Department of Vaccines at the National Public Health Institute in Helsinki, will discuss the FinOM trial that was conducted in Finland, and then Steve Black will come back and discuss otitis media from the Northern

California Kaiser Permanente trial. And then I'll give brief conclusions at the end on impact.

First of all, a quick background on clinical manifestations of otitis media or rather of pneumococcal disease in general. This pie diagram shows you the major pneumococcal syndromes and makes the point that the pneumococcus is a very important if not the most important single pathogen contributing to major bacterial infections in U.S. children, causing 45 percent of meningitis in the first two years of age, a vast majority of bacteremia sepsis, and for these two Prevnar is indicated in the package insert, but also about 60 percent of pneumonias and as much as 40 percent of bacterial otitis media.

This shows you a pyramid which puts into perspective the relative frequencies of these syndromes. Fortunately the most severe of those syndromes are the least common, with about 1,400 cases in children under five years of age of meningitis, 17,000 of bacteremia, and estimated 71,000 for pneumococcal pneumonia.

But at the base of this pyramid and really a massive number is the five million estimated episodes of otitis media each year, and although clearly a much milder disease than the others, it certainly has morbidity and has a very tremendous impact on health care and antibiotic use and so forth.

With regard to the epidemiology of otitis media, these are actually data from the Northern California Kaiser

Permanente trial and the control groups looking at the age distribution of otitis media, and which show several things.

One, that in boys, in blue, the rates are somewhat higher throughout follow-up period, here to 42 months of age, than in girls. And the peak incidence is very high, and this is otitis visits per 100 children-months between six and 18 months of age, but really continues throughout the follow-up period, declining slowly but steadily with time.

A somewhat more extended age distribution comes from these data, which plot the number of visits for otitis media to physicians' offices in thousands by year from zero to ten years of age, and you can see that the peak here is 4,400,000 visits, and again, a decline over time, but continuing to have as many as five to 600,000 visits per year even out to ages nine and ten years of age.

So to summarize the impact of otitis media, this is the most common reason for sick child visits. It is also the leading cause for prescribing antibiotics during childhood, and we believe that the use of antibiotics frequently contributes to the increasing antimicrobial resistance that we have seen in this country and elsewhere.

Complications of recurrent disease and effusions lead to tempanostomy tube insertions, and this is the most common reason why children have surgery that requires general anesthesia.

The direct and indirect annual costs have been estimated to exceed more than $5 billion per year in children under five years of age. That's for all otitis media.

And this just shows you, I think, what we all know, and that is during the '90s there has been a progressive increase, looking here at pneumococcal disease, an increased rate of resistance from the low digits, five percent or so, to over 30 percent at the end of the decade.

An interesting question is whether there will be an impact of Prevnar on this phenomenon.

Importantly, the serogroups that are most likely to be resistant to penicillin and other antibiotics are serogroups that are contained among the seven valent types of the vaccine, six, 14, 19, 23, and nine. And that's true not only in the U.S. but throughout the world.

And specifically in terms of coverage for otitis media, this is an example of a study by Ellen Wald's group in Pittsburgh reasonably recently looking at serotype distribution in otitis media and suggesting a coverage of the vaccine serotypes themselves of about 70 percent.

If you assume coverage for cross-reactive types, that goes up to 85 percent, and if you only selected antibiotic resistance, you would probably get up over 90 percent in this series in terms of coverage by the vaccine types and related types.

So at the moment, you my be aware that the package insert makes no mention whatsoever about otitis media with regard to Prevnar efficacy, and we are here today to propose that otitis media be included in the package insert and that the indication be that Prevnar is indicated for active immunization of infants and toddlers against invasive disease and otitis media caused by Strep. pneumoniae due to the capsular types included in the vaccine.

And some of the reasons why we believe this is to be important is that there are now two randomized, well controlled trials that you'll hear about which show statistically significant decreases in otitis media outcomes.

Secondly, you'll hear that Prevnar immunization does have an important medical effect on otitis media disease and its implications, and that we believe it's important that this information, since it's now published and talked about in the literature, be accurately described in the label so that we can communicate appropriately information to physicians and to parents.

The trials that you will hear about just very briefly are the FinOM efficacy trial, the major trial that has been reported in the New England Journal under the direction of Juhani Eskola and Terhi Kilpi who's here with us today, and then a follow-up trial focusing most clearly on tempanostomy tube placements in Finland in the follow-up period, which Terhi Kilpi

will describe.

And then Steve Black and Henry Shinefield will present the data updated on the Kaiser Permanente trial.

The two trials, just to contrast them, really they're quite different, but they give complementary data. The FinOM trial, of course, done in Finnish infants receiving a U.S. schedule of vaccination, a relatively smaller number of children, 1,600 or so, but I think what's very special about this trial is that myringotomies were performed, and we have culture specific diagnosis of the etiology of acute otitis media.

In contrast, the Kaiser Permanente trial was much larger, more than 37,000 children, Northern California. The diagnosis was made clinically rather than in a standardized way on a routine basis by hundreds of physicians and was captured from the automated databases at Kaiser.

And with that I'll ask Dr. Terhi Kilpi to come up and tell us about the FinOM studies.

CHAIRMAN DAUM: Before he does that or she does that -- I'm sorry -- does the committee want to ask any clarifying questions about Dr. Siber's presentation? Data that were unclear?

(No response.)

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

Dr. Kilpi, welcome.

DR. KILPI: Good morning. I'm going to present the main efficacy results of the Finnish otitis media vaccine trial that evaluated the efficacy of two seven-valent pneumococcal conjugate vaccine for prevention of acute otitis media due to vaccine serotypes in children less than two years of age.

And this study was conducted in the Tampere area in Finland, and the clinical phase started in December '95 and ended in March '99, and during this time, we had almost 2,500 children were enrolled in the study. This is approximately 55 percent of the birth cohort in the area.

And all of these children were randomized to receive either one of the two pneumococcal conjugate vaccines used in the study, the PncCRM vaccine labeled, licensed as Prevenar or the PncOMPC vaccine or the control vaccine that was Hepatitis B vaccine in our study.

And the children received these vaccines at the age of two, four, six, and 12 months. They were followed in study clinic setting from two months to 24 months of age, and during the follow-up every effort was made to have all respiratory infections according to these children requiring medical attention evaluated and treated at the study clinics by our study physicians.

This trial was specifically designed to study otitis media, and therefore, we needed a definition for acute

otitis media, and we defined that there has to be symptoms of acute infection and signs of inflammation in the middle ear.

And whenever acute otitis media meeting this definition was diagnosed at the study clinic by our study physician, myringotomy was performed and middle ear fluid aspirated for bacterial culture, pneumococcal serotyping when appropriate, and pneyumolysin PCR.

Otitis media is a condition that tends to recur in a proportion of individuals over and over again, and we, therefore, wanted to analyze the vaccine efficacy by all AOM episodes rather than just the first ones, and we, therefore, needed a definition for an episode.

And we defined that it starts at diagnosis and lasts for 30 days. And these were the endpoints we looked at, and these were defined in the protocol and in the analysis plan. The primary endpoint was all AOM episodes due to vaccine serotypes.

The secondary was first and subsequent AOM episodes due to vaccine serotypes, and we also looked at all pneumococcal AOM episodes, at all AOM episodes, and recurrent AOM.

We have late also performed some additional analysis, looked at endpoints of special interest, namely AOM episodes due to vaccine related serotypes, due to serotypes unrelated to vaccine types, and also calculated the vaccine

efficacy against AOM episodes due to individual pneumococcal serotypes.

And from now on, I will present the results for the PncCRM group of this study as compared to the control group and forget about the third arm since this is the vaccine we're talking about today, and to start with, I hope this slide will demonstrate to you that our trial was very successfully conducted.

Of the 1,662 children enrolled in these two groups, as many as 1,580 completed the trial without critical protocol violations. That is, 95 percent of the children originally randomized. So we feel pretty comfortable with the results.

And now to the results. During the protocol follow-up period that lasted from 6.5 to 24 months of age, there were 107 AOM episodes due to the vaccine serotypes in the PncCRM group as compared to 250 episodes in the control group.

And this means that the vaccine efficacy against the primary endpoint, all AOM episodes due to vaccine serotype was 57 percent, and this efficacy was statistically significant as indicated by the confidence interval here.

And to the secondary analysis, the vaccine efficacy against AOM, first episodes of AOM due to vaccine serotypes was 52 percent, and the vaccine efficacy in the subgroup of children who had already had one AOM caused by the

vaccine serotypes was 48 percent. So the vaccine does provide protection even if a tad failed one.

And this is a summary of the main efficacy results, AOM, vaccine efficacy against AOM due to vaccine serotype, 57 percent; against culture confirmed pneumococcal AOM, 34 percent; against pneumococcal AOM confirmed by either culture or PCR, analyzing PCR or both, 20 percent. These are all statistically significant. Against any AOM, six percent, and recurrent AOM, 16 percent. The latter two failed to reach statistical significance in our study.

And these were the analyses for the protocol analysis, and this is the same for the intention to treat analysis and for the intention to treat follow-up period that started already at two months of age.

And as you can see, the results are very similar to the protocol analysis. What may attract attention in these efficacy results is the different efficacy the vaccine provided against culture confirmed pneumococcal AOM as compared to pneumococcal AOM confirmed by either culture or PCR, and therefore, we have looked at this issue a bit more closely and found that the vaccine does not provide any protection against chemical culture, negative but PCR positive AOM, and this explains the difference between these two entities.

And since the PCR method we used in our study was quantitative or perhaps more precisely semi-quantitative, we have

also been able to look at the PCR counts in the pneumococcal culture negative cases of AOM as compared to the Pnc culture positive cases and found that the PCR counts are considerably higher if the pneumococcal culture is positive than if it's negative.

So whatever the significance of PCR positivity in the pneumococcal culture negative cases of AOM is, it certainly does not seem to be a sign of active pneumococcal disease.

The design of the FinOM vaccine trial allowed us to characterize the vaccine efficacy a bit further because we had the culture results from each even of otitis media and we had the serotyping results. And one of the things we were interested in was if the vaccine provided the same kind of efficacy or different kinds of efficacy against AOM caused by individual vaccine serotypes, and this is what we found.

The efficacy against AOM caused by 6B was excellent. The point estimate is 84 percent. It's good against AOM caused by 23F and 14 point estimates, from 60 to 70 percent, but rather modest for AOM caused by Type 19F, point estimate being only 25 percent.

When we designed the trial and decided to have AOM caused by the vaccine serotypes as our primary endpoint, we knew that we could anticipate that the vaccine might protect also against other than vaccine, against AOM caused by other than vaccine serotypes only, and that is the relative serotypes to the

vaccine serotypes, and therefore, we have also wanted to look at this and we found, indeed, that there were 41 AOM episodes caused by the vaccine related serotypes in the PncCRM group as compared to 84 episodes in the control group, and this means that the vaccine efficacy against AOM due to the vaccine related serotypes is 51 percent, which is almost as good as the efficacy against AOM caused by the vaccine serotypes themselves.

However, when we come to the other serotypes, the non-vaccine, non-vaccine related serotypes, we see in excess of 30 episodes caused by these serotypes in the PncCRM group as compared to the control group, which translates into a negative efficacy of minus 33 percent in the vaccine group as compared to the control group, and this difference almost reached statistical significance.

However, the bottom line is that the vaccine provides protection against any culture confirmed pneumococcal AOM and reduces it by 34 percent.

And this is now vaccine efficacy against AOM caused by the two most common cross-reactive serotypes, 6A where the point estimate is 57 percent and 19A where the point estimate, 34 percent, actually is even a little higher than for the vaccine serotype 19F itself.

So conclusions from this trial follow-up part are the the PncCRM vaccine is efficacious against culture confirmed vaccine serotype specific, active otitis media, culture

confirmed AOM due to the vaccine related serotypes, and culture confirmed pneumococcal AOM.

And now I will move on to the extended follow-up. We have recently collected additional information on the children enrolled in the PncCRM and control groups to assess the long-term effects of the PncCRM vaccine on pneumococcal carriage, antibody persistence, and surgery due to otitis media in the routine practice when those children had completed the trial follow-up.

And I will now present the results for this category as specifically the effect of the vaccine on the incidence of tympanostomy tube placements up to four to five years of age.

I will also briefly present some results for the other two categories.

And this extended follow-up was carried out by inviting the children to a single follow-up visit in spring 2001 when they were at the age of four to five years. And we invited altogether 1,490 children. They represent 90 percent of the original study population, and these were the children who had completed the ITT follow-up and who were still living in the Tampere area.

And 756 of these children followed the invitation and were evaluated at the study clinic in spring 2001, and since these children only represent 45 percent of the original study

population, we have also collected information on the tympanostomy tube placement of these children, these 1,490 children to be able to feel comfortable with our tympanostomy tube results.

And I will now show you what kind of data we have available on the tympanostomy tube placements of these children and for which categories of children we have this date.

So, first, the analysis populations. Initially all children were followed from two to 24 months of age in the study clinic. So we had 1,662 children at the beginning and 65 of them dropped out during the trial. So at the end we had 1,597 children, and of these, 107 had moved out or the Tampere area after they completed the follow-up in the trial setting.

So we had, 1,490 children still living in the area, and these children constitute the eligible children, the analysis' population two.

Then we have this subgroup of children, the 756 fully evaluated children, and they constitute the analyst population one, and for this part of children, we have completed tympanostomy data available, and for this part of children, we have the hospital tympanostomy tube data available.

And tympanostomy tube placement in the FinOM follow-up study were ascertained in the following way. For the fully evaluated children, we could ask the parents if the child had had tubes placed after completing the trial follow-up and

then confirm the parents' answers by reviewing the hospital records collected from the area hospitals and by reviewing the medical records requested from private physicians.

And it turns out that 78 percent of the tympanostomy tube placement had been performed in public sector hospitals and 22 percent in private medical centers.

For the eligible children we had the hospital records from the area hospitals which are likely to represent approximately 80 percent of the tympanostomy tube placement performed in these children after they completed the trial follow-up.

And before I go to the results, I think I need to explain to you what kind of practices were followed during the vaccine trial and after it when the children returned to normal life, to the real life situation.

During the trial, tube placement, if considered indicated, was included in the study services. They were almost exclusively performed at the Tampere University hospitals. They were free of charge to the patients, and the hospital guaranteed access to treatment within four to five weeks of referral.

When the trial follow-up was over, the children returned to normal life, and in the real life situation in Finland if tube placement is considered indicated, there are two options, two possibilities to have it performed. It can either be done in public hospitals where the charge is nominal, but

waiting time can be from three to four months, or it can be performed in private medical centers that charge ten times that of their public sector charge, but there is no waiting time.

And so principally, the indications for tympanostomy tube placement were the same during the vaccine trial and after the trial when the children had returned to the normal life situation, but access to treatment became definitely more difficult when the trial follow-up was over due to the reasons here.

And this makes plain why the incidence of tympanostomy tube placements in the FinOM children during the vaccine trial follow-up was considerably higher than what it is in the children of the same age in Finland in general.

And it also makes plain why this incidence of tympanostomy tube placement dramatically dropped when they returned to a normal life situation. So it appears that milder cases of recurrent AOM and otitis media with effusion were treated with tympanostomy tube placement during the trial and after it, and this makes plain why the effect of the vaccine on the incidence of tube placement was different here from what it was here.

Okay. Now I'll go to the results, and we'll just remind you that I'm going to present them for the full evaluated children analysis population one and for the all eligible children analysis population two.

And these are the tympanostomy tube placements in the fully evaluated children. During the trial follow-up from two months to two years of age, 20.3 percent of the children in the PncCRM group as compared to 23.8 percent of the children in the control group had tympanostomy tubes place, and the incidence rate of events is here.

So the difference between the vaccine group and the control group is 12 percent, and this is not statistically significant.

However, when the normal life situation started during the period from two years to four to five years, only 8.2 percent of the children in the PncCRM group as compared to 13 percent of the children in the control group had a tympanostomy tube placement. The incidence is shown here, and the conclusion is that the vaccine reduced tympanostomy tube placements during this age period of time by 39 percent, and this difference is statistically significant.

And since we have only 45 percent of the original study population in these fully evaluated children, it was, of course, important to see if the results are the same for all eligible children for which we had the public sector hospital data available. And so now only the tympanostomy tube placements performed in the public hospitals are included in this slide.

And here the difference during the trial follow-up is even smaller. It's only four percent, but, again, during the

normal life follow-up from two years to four to five years of age we see a reduction of 44 percent in the incidence of tympanostomy tube placements in the PncCRM group as compared to the control group.

And even the lower limit of the 95 percent confidence interval is as high as 19 percent.

Now, this shows the same thing for the fully evaluated children graphically. This is the cumulated hazard for tympanostomy tube placement, and as you can see, there is practically no difference during the trial follow-up up to 24 months of age, but after, as soon as they return to normal life, the curves start to part and continue to do so.

So there is no sign of waning efficacy here. And this is the same thing for all eligible children, and again, the same pattern.

I will now show briefly kinetics of antibody concentrations for three of the most serotypes causing AOM in our study, and I think that these curves are beautifully consistent with the persisting efficacy I have just demonstrated.

This is the antibody concentrations for 23F, and as you can see, the level is the same at the age of 24 months and then at the age of four to five years.

For serotypes 19F and 6B, the antibody levels even seem to increase a little.

And this is data collected at the follow-up visit

in spring 2001. We asked the parents if the child has had AOM after 24 months of age, and according to the parents of the children who received the PncCRM vaccines, 67 percent of these children had had AOM after completing the trial follow-up as compared to 72.7 percent of the children in the control group.

At the visit, 11.4 children in the PncCRM group as compared to 12.5 percent in the control group had middle ear abnormalities, and 8.5 percent of the children carried vaccine serotypes as compared to 13.6 percent of the children in the control group, and this last differences is statistically significant.

So these last data is consistent with the conclusions that PncCRM reduces tube placement due to otitis media, and that the vaccine efficacy against otitis media persists for years.

Thank you.

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

We have a few moments for clarifying questions. Dr. Griffin.

DR. GRIFFIN: After the study was completed, did the parents and the physicians know who had received vaccine and who hadn't? I mean was the blind broken and they were informed as to whether they had been immunized?

DR. KILPI: Yes. The code was broken in August '99, and the parents were informed about the vaccine their child

had received in October '99, and so I guess you are wondering if this fact may have affected the results we received after the completion of the trial, and we looked at this.

DR. GRIFFIN: You just wondered whether physicians say, "Oh, well, they were vaccinated. So they wouldn't need this"?

DR. KILPI: Yes, yes, and that's why we have looked at the incidence.

Yes, because many children completed the trial follow-up long before the code was open, some of them even had two years of follow-up after the code was revealed to the parents. So we looked at the incidence of tube placements after the completion of trial follow-up, but before unblinding, and this is the incidence in the PncCRM group as compared to the control group, and this is the total.

And this is for fully evaluated children and this is for all eligible children. So I think there is no sign that unblinding would have affected the results.

CHAIRMAN DAUM: Thank you.

Dr. Diaz, then Dr. Katz, and Dr. Schwartz.

DR. DIAZ: Dr. Griffin asked my question.

CHAIRMAN DAUM: Dr. Katz, please.

DR. KATZ: On the schedule of both groups, were they also receiving Haemophilus Influenza B conjugate vaccine at the same time? I don't mean necessarily the same visit, but this

was part of their routine?

DR. KILPI: Yes, yes. The concomitantly given vaccine was also DTP Hib combination that they received at the age of two, four, six -- of six months, and we used two different DTP Hib combination vaccines.

DR. KATZ: I guess I wondered why you picked Hepatitis B as the control vaccine. What was the motivation for that?

DR. KILPI: Well, it's not included in the routine program in Finland. It's only recommended for risk groups, and it seemed to be the right thing to do to offer something to the control group also, something beneficial.

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

DR. SCHWARTZ: I'm confused or at least I don't understand.

CHAIRMAN DAUM: Turn you mic on. You push that button on the base.

DR. SCHWARTZ: Yes, sorry.

When you did tympanocentesis in that group of patients, whether they were on control or on the study vaccine, was the tympanocentesis 80 percent of all episodes or as close as you could get to every single episode on the study trial or after the first tympanocentesis that yielded a pneumococcal serotype of any serotype, then that child did not have to undergo further

tympanocentesis and yet remain on the study?

DR. KILPI: No. It was the first one, in the first way. So whenever they had AOM diagnosed, myringotomy actually was the procedure we used. It made a small hole and suction. So it was performed every time AOM was diagnosed, at every single visit.

Of course, this was not 100 percent. It was saying from 93 percent of the visits when AOM was diagnosed.

DR. SCHWARTZ: So some children could have undergone six procedures or five procedures during this study?

DR. KILPI: I'm afraid so.

CHAIRMAN DAUM: Thank you.

Dr. Overturf and Dr. Stephens.

DR. OVERTURF: I wondered on the organisms that came from both the vaccine related serotypes as well as the organisms from the non-vaccine related serotypes whether you had any antibiotic susceptibility data on either one of those groups as compared perhaps to the serotype from the vaccine.

Do you have that data?

DR. KILPI: We do. We looked at -- what we have in the database is the data on penicillin resistance, but the resistance situation in Finland is very different from that in the U.S. So that almost all of them were susceptible to penicillin.

However, if they were not susceptible they were

usually or I think they were exclusively vaccine serotypes.

CHAIRMAN DAUM: Thank you.

Dr. Stephens and then Dr. Decker.

DR. STEPHENS: Two questions. One had to do with the PCR count data. Can you give us a better understanding of that in terms of organisms per mL, presumably in terms of those counts.

DR. KILPI: I'm afraid I can't. As I told you, this method is semi-quantitative. We have now developed also using a better PCR method that allows quantification in a better way. This was just to demonstrate that obviously this huge difference tells us that it is the PCR negative case -- PCR positive, culture negative cases are something different from the culture positive case.

DR. STEPHENS: Okay. Can you also provide any information regarding the serotype replacement issue? That is, is there a difference between non-vaccine serotypes?

You gave us the data that there was a significant difference between vaccine serotypes. Is there an increase in non-vaccine serotypes in terms of carriage?

DR. KILPI: In terms of carriage? Yeah, well, I have some carriage data here.

(Pause in proceedings.)

DR. KILPI: So, well, this is first to show that the vaccine does not have effect on the overall carriage of

pneumococcus. This is the other carriage figures at the age of 12 months, 18 months, and four to five years in the PncCRM group as compared to the control group. So always it's approximately the same proportion of children that are carriers.

And then this shows the carriage rates at 12 months of age, and actually there we did not see any statistical differences in these three categories. So there was perhaps a small reduction of the carriage of vaccine serotypes, but this is not statistically significant, and these are also pretty much the same.

This is different from the rate that is obtained in the developing countries. So the effect of the vaccine seems to be different. The effect of the vaccine on carriage seems to be different in developing country situations than in an industrialized country perhaps.

And here we have the carriage rates at the age of 18 months, and there is clear reduction in the carriage of vaccine serotypes. Cross-reactive serotypes are approximately even, and there is replacement by the non-vaccine related serotypes.

And when we come to the age of four to five years, again, we see the reduction in the carriage cell vaccine serotypes, and this time the situation for the other serotypes is even, but there is a small increase of the carriage of the cross-reactive serotypes in the PncCRM group as compared to the control

group. However, these differences are not statistically significant.

CHAIRMAN DAUM: Thank you.

Dr. Decker.

DR. DECKER: No questions.

CHAIRMAN DAUM: Dr. Whitley.

DR. WHITLEY: This is an obvious question, and logically antibiotic usage would be lower in the vaccinated compared to the control population. Do you have data to support that logical assumption?

And specifically what I'm trying to get at is was there extraneous antibiotic usage in the vaccinated compared to the non-vaccinated group?

DR. KILPI: I don't have any slides to support that, but the number of antimicrobial prescriptions in the vaccine group was lower than in the control group, and I think it is covered in the FDA presentation.

CHAIRMAN DAUM: Okay. We have time for two more comments. Dr. Faggett.

DR. FAGGETT: Thank you. This is valuable clinical data.

Question number one, do you have national health insurance in Finland?

And Part 2 of my question: what were the criteria for tube placement? It would appear that with decreased costs

and increased access that might impact on decisions to have the tube placement.

DR. KILPI: Yes, we do have national health insurance in Finland, and this basically means that the public sector is free of charge or the charge is only nominal, and for the private care, the children get reimbursed for the treatment.

So part of the sum is paid back, but anyway, the cost is considerably more to the parents than what would be in the public sector.

And the indications for tube placement, the recommended indications, I think, are pretty much the same as in the U.S. It's recurrent AOM, three to six episodes per six months or persistent otitis media with effusion.

But of course, as everyone knows, I think, that in a trial situation when it is really followed that this happens, it's different than if parents and doctors make individual decisions based on the waiting list and the financial situation of the family.

CHAIRMAN DAUM: And the age.

DR. KILPI: Yes.

CHAIRMAN DAUM: Dr. Glode.

DR. GLODE: I just wanted to clarify the original entry criteria. I know I read in the briefing materials that the public health nurse gave the vaccine and enrolled the patient in the study initially at two months of age or whatever; is that

correct that that was generally done by public health nurses?

DR. KILPI: Well, they are public health nurses by training.

DR. GLODE: Yes.

DR. KILPI: They were trial staff. It's the policy in Finland that nurses vaccinate, and they were hired -- they were part of our staff team. So it was not their normal public health nurses, but it was a vaccinator we had hired for the trial.

DR. GLODE: Okay, and they knew which vaccine they were giving?

DR. KILPI: No. No, they didn't.

DR. GLODE: Okay. They were blinded.

DR. KILPI: Well, the vaccines were letter coded, and there was six letter codes for the three vaccines, and the vaccinator knew naturally which letter code the child received, and they were, therefore, kept separate from the other staff so that the staff didn't even know which letter code was assigned to each child, and this was never recorded anywhere.

DR. GLODE: Okay. Thank you.

CHAIRMAN DAUM: I'm going to take prerogative for the last question.

You showed some antibody data between the Prevnar vaccinees and the hepatitis vaccinees for several of the serotypes. Do you have similar data for Type 19F?

DR. KILPI: I showed for 19F.

CHAIRMAN DAUM: Did I miss it?

DR. KILPI: Yeah, it was --

CHAIRMAN DAUM: I'm sorry.

DR. KILPI: It was increasing also.

There.

CHAIRMAN DAUM: So I guess the question is then in light of the relative poor efficacy against that serotype, what do these kinds of data mean in terms of inferring protection?

DR. KILPI: Well, especially when it comes to 19F, it's very, very difficult to make any conclusions from the antibody concentrations and try to correlate to the efficacy. Obviously, these are antibody concentrations that look rather good anyway. Not a very good efficacy can be reached against otitis media.

CHAIRMAN DAUM: Thank you very much.

I think we now must move on to the next part of the sponsor's presentation, which would be Steve Black again to tell us about the Kaiser trial efficacy.

Thank you very much, Dr. Kilpi.

DR. BLACK: Thank you, Dr. Daum and everyone.

What I'd like to do now is present results on otitis media from the Kaiser Permanente efficacy trial. Otitis media, as well as pneumonia, were also outcomes apart from invasive disease there, and what I will show you are the results

from our trial, which I think you'll agree are remarkably consistent with those presented from Finland.

To remind you, the pre-licensure trial was a randomized, double blind, controlled trial with one-to-one allocation, and the control vaccine used in this trial was meningococcal C conjugate vaccine, and as in Finland, immunizations were given at two, four, and six months of age, with a booster dose at 12 to 15 months. And these were given concomitantly with routine childhood vaccines.

The trial began in October of 1995 and was unblinded in April of 1999.

So otitis media outcomes were identified quite differently than in Finland. Diagnoses were made by the patient's regular pediatrician as part of routine care and in both the emergency room and in the clinic, and as part of routine care, optically scannable forms are used which capture out-patient diagnoses, and otitis media is one of these.

There's no cross-training of these observers.

Surgery for ear tube placement was captured as part of our hospital database, and this is exclusively performed in either surgical centers or hospital within our program, and spontaneously draining ears were cultured during the trial as well.

The primary endpoint was all otitis media episodes, and an episode was defined as a visit for otitis media

with no prior visit within 21 days. It's important here to realize that if a child has an otitis media visit every 18 days, this can go on for months and still only count as one episode.

And this in retrospect was not such a great idea, but it does blunt the effect that we see for episodes against frequent disease or more severe disease.

The secondary endpoints were first otitis media episode, frequent otitis defined in Finland as three or more episodes within six months, four or more within 12 months; tympanostomy tube placement with spontaneously ruptured ears due to vaccine serotypes; and clinic visits for otitis media.

Just as a frame of reference here, which I find useful, is that for all episodes we estimate that 50 to 60 percent are bacterial. Of those, probably 40 percent in the United States are pneumococcal; 75 to 85 percent, as Dr. Siber showed, are vaccine serotype or cross-reacting. So that the potential overall impact of 100 percent efficacious vaccine against all clinical episodes of otitis media is in the range of eight to 20 percent.

Now, there are two data sets that were submitted vis-a-vis otitis media. Two analyses were performed. One was submitted as part of the PLA, included data through April 30th of 1998.

However, after that time, blighted immunization per protocol continued. The study nurses, the physicians, and

the parents, the investigators were unblinded on April 20th of 1999, and there's a second analysis on otitis media there.

These compare these two analysis points just to give you an idea because the population dynamics change pretty dramatically during the year. You can see that the total number enrolled is about 17,000 in each group as of the initial analysis, and that enrollment was stopped in August of 1998. So the enrollment really had not progressed that much by past that point.

However, the number of booster doses is substantially higher in the second analysis, reflecting the fact that the children are now aging rather than just being enrolled, and the number over age two, there was substantial numbers in the initial analysis, but no children over age three. And you can see the number over age two in the second analysis is almost triple and that there are substantial numbers of children over age 3 in the second analysis.

This gives you an idea of the number of events. Otitis media, as has been pointed out, is much more common than invasive disease, which allows us to detect the efficacy that we did, and you can see here that in an intent to treat analysis, there are more than 116,000 visits for otitis media, almost 85,000 episodes, as compared to these numbers in the initial presentation.

Where this becomes especially important is for the

less common outcomes here: frequent otitis media or especially for ear tubes where we have much more statistical power in the second analysis.

This is the protocol analysis first, and the two different analysis periods, and first you can see these are very similar between the two for otitis media episodes, the seven percent effect in 1998, 6.6 percent effect in 1999 for visits, 8.9 percent versus 7.9 percent, and for frequent otitis media, apart from the change in the number here, you can see that there's more precision or titer confidence interval as well, an 11.6 percent reduction for frequent otitis media in this population as of the final analysis.

This is the intent to treat analysis, and the numbers are a little bit lower. We were attempting, although the trial was not designed to do myringotomy because we couldn't get our pediatricians or ENT people to do that, we were able to come up with a surrogate outcome to look at vaccine serotype specific effect here, which was spontaneously ruptured tympanic membranes.

It's important to realize this is a different disease really than just acute otitis media, but nonetheless allows us to look at vaccine serotype specific effect, which is shown here. In the initial analysis these numbers were not statistically significant, but are here especially in the intent to treat analysis where we have 66 percent reduction of vaccine serotype spontaneously ruptured eardrums with a much tighter

confidence interval, and these results are consistent with a vaccine serotype specific effect in Finland.

A question was brought up by Dr. Whitley regarding antibiotic use, and we did collect data on that. I'm glad we put this slide in sine you asked the question, and this shows -- the way this is groups, these are what was recommended for fist line antibiotic use in our program for otitis media, and you can see that constitutes the majority of the prescriptions.

There was a five percent reduction in that use in our population, really not surprising since otitis media is probably the most common cause of antibiotic use.

For second line drugs, which are shown here, Augmentin and all of these, there's about a ten or 11 percent reduction, basically extremely consistent with the frequent otitis reduction that we saw in the trial.

So the children who were going on to have more complicated or extensive otitis media, our interpretation is here that there is a reduction that's consonant with that in terms of antibiotic use.

There's an overall reduction here of 5.3 percent, and these drugs are still used for prophylaxis, for frequent otitis media, and we see a somewhat higher effect here as well.

So our conclusion from our studies is that Prevnar significantly reduced the risk of otitis media in our trial, and the efficacy was higher for frequent otitis and for ear tube

placement.

So thank you, and I'd be happy to answer any questions.

CHAIRMAN DAUM: Thank you, Dr. Black.

We have a few moments for committee questions. Dr. Goldberg.

DR. GOLDBERG: Can I just ask a clarification? The otitis media endpoints are secondary endpoints from the original trial where the vaccine was approved for invasive disease. Can you just clarify for me in the original analysis plans and in the protocol were you thinking about using the same methods that you're using now?

Was that how the data was analyzed? And were there any adjustments made in any of these analyses for the '98 analysis on otitis media compared with the '99 one?

It's just for clarification, please.

DR. BLACK: Sure. The initial protocol specified otitis media episodes as the primary endpoint and also specified endpoints, other secondary endpoints as well.

The interim analysis in '98 was not really a decision point analysis. It was basically conducted at that point in time because we were analyzing the invasive disease at that point and to present that data, but we were not requesting a decision at that point for otitis media. So we did not apply a decision rule correction there.

CHAIRMAN DAUM: Thank you.

Dr. Parsonnet and then Dr. goldberg and Dr. Schwartz.

DR. PARSONNET: Yeah, I have a few questions. Can you just give me a sense of what the overall incidence of otitis was, annualized incidence in the two groups?

DR. BLACK: Yes. The average child in the control group -- and the numbers are very similar because of the differences there -- had about one and a half visits of otitis media per year, which is very consistent with national and published information.

DR. PARSONNET: And just along with that, I was just wondering if you have any sense for what the accuracy of the diagnosis was among your clinicians.

DR. BLACK: Well, you know, there were two approaches here that were taken to this outcome. One is the approach that was taken in Dr. Kilpi's trial, which is, you know, an extremely rigorous validation here.

What we were looking at in our trial was, to use Dr. Kilpi's phrase, the real world impact here, and we really didn't cross-train our observers. We think that that probably reduced the sensitivity of our finding because like in our setting as in others, the individual physicians have different criteria for otitis media, not all of them are assessing the mobility of the tympanic membrane. Some are just looking for

redness.

So it's nonspecific, but it, we think, represents the real world picture as pediatricians. We don't think our pediatricians are really different from others for diagnosing otitis media in the rest of the country.

DR. PARSONNET: So then the last follow-up is actually related to that, which is the tympanostomy tubes are placed. Are they usually placed by pediatricians or are they placed by ENT docs.? Is that so you would be more likely to have a real accurate diagnosis in the tympanostomy?

DR. BLACK: Well, the tympanostomy tubes are all done in house in the hospital under general anesthesia by ENT physicians, and the rate of tube placement in our population is relatively low. It's about one percent, which is low even for this country.

But we know that all of those children -- you know, if you look at the average number of visits the children had prior to coming in for tube placement, it's between five and six.

Does that answer your question?

DR. PARSONNET: Yes.

CHAIRMAN DAUM: Dr. Goldberg, and then Dr. Schwartz and Diaz.

DR. GOLDBERG: Can I just get an additional clarification on your answer to the question that I asked?

In your original trial, it was designed for otitis and for invasive disease, correct?

DR. BLACK: Correct.

DR. GOLDBERG: Then you have two major endpoints as I see it. Sorry. I just want to make sure I --

DR. BLACK: Well, three. Actually pneumonia as well, but we're not talking about that.

DR. GOLDBERG: Well, okay. That even takes my question one step further then.

My question really is: did you at any point when you did -- was the original protocol written using the analysis methodology that you're using now?

And if so, was the invasive disease considered as one of those multiple endpoints?

DR. BLACK: Yeah.

DR. GOLDBERG: And what might the impact have been or --

DR. BLACK: Let me ask a statistician to address your questions.

DR. GOLDBERG: Thank you. It would just help clarify my thinking.

Thank you.

DR. BLACK: Bob Kohberger from Wyeth.

DR. KOHBERGER: The pre-specified plan before anything was unblinded, the first stage was invasive disease,

which is tested at .05. If that was significant, we went on to the second stage, one of which was otitis media, all episodes.

If that was significant at .025, we then would go on to all those multiple secondary endpoints. So we adjusted for this multiple hypotheses.

In terms of the databases, the official database was 1998. We closed the database, cleaned it up, and that was what was submitted to FDA. The '99 data is primarily confirmatory of what we did in '98.

Does that answer your question?

DR. GOLDBERG: Had your original analysis plan included the one that you're using now?

DR. KOHBERGER: It's exactly the same.

DR. GOLDBERG: That's my question.

Okay. Thanks.

CHAIRMAN DAUM: Let's move on please to Dr. Schwartz.

DR. SCHWARTZ: I'll pass.

CHAIRMAN DAUM: Dr. Overturf or Dr. Diaz -- excuse me -- was next.

DR. DIAZ: Thank you.

Just a couple of questions in regards to the tube placement group of children. You commented that tube placement in your practices is lower than generally in other practices, and I was curious about several things.

One is the total numbers of children that we're talking about that went on to tube placement.

Secondly, if you have any data that looks at the timing for tube placement for children, i.e., prior to unblinding of the study.

And, thirdly, if the criteria for tube placement in children in the younger groups -- have you looked at any validation as to the use of criteria for tube placement across age groups?

DR. BLACK: Yeah, okay. There are several questions there. I'll see if I can remember to answer all of them, and if I don't, please remind me.

DR. DIAZ: Sure.

DR. BLACK: I think this gives you an idea as to the total number of events here. This slide shows you the number of children who had tube placement in the intent to treat and the protocol analysis at the two points in time.

So remember there are about 38,000 children in the population. So this is a little bit more than one percent, and this is about two percent here by the time the second year is added in.

You know, the criteria for using this, the pediatricians are free to refer to the ear, nose, and throat people for evaluation really at any time, but the tubes are normally put in if there is documented, persistent effusion with

hearing loss or if there are multiple episodes, and the stated criteria are three or more within six months, four or more within a year.

But the average number actually that the children had was higher than that in this trial and in our practice in general.

DR. DIAZ: And also the differences or any data regarding tube placement prior to our after the unblinding of the study.

DR. BLACK: After the unblinding of the study in April of '99, we stopped following these children for tube placement, but we don't really have any reason to -- unlike the trial in Finland where separate study physicians were set up to evaluate the patients and there was a separate clinic, the children really were evaluated in standard care whether they were in the trial or not during the entire time period, and we would presume afterwards.

CHAIRMAN DAUM: Now, Dr. Overturn, thank you for being patient.

DR. OVERTURF: Steve, on your slide on the overall number of oral antibody prescriptions, I assume this was all antibodies or prescriptions, or was it only antibody prescriptions for otitis media?

And if so --

DR. BLACK: No, these are all antibiotics.

DR. OVERTURF: What proportion of oral antibiotic prescriptions are written for the indication for otitis media?

DR. BLACK: Yeah, we've actually not looked in this analysis. Our pharmacy for economic reasons has looked, and it's depending on age of the child. In the younger children, the two year old range, the toddler range, it's about 90 percent.

So the concordance here between antibiotic use and the otitis media effect is probably due to the fact that we're looking at the same thing in two different ways.

DR. OVERTURF: Do you know what proportion of otitis media patients received antibiotics?

DR. BLACK: That's something that's changing over time. Still the majority of them do receive that in the young age groups under two.

Over two the sort of watchful waiting is becoming increasingly more popular. I'm sorry I can't quantitate that for you.

CHAIRMAN DAUM: Ms. Fisher and then Dr. Stephens.

MS. FISHER: I just want to get this straight. In this study, all otitis episodes were reduced by seven percent in the Prevnar group, correct?

DR. BLACK: Correct, yes.

MS. FISHER: Well, your conclusion is that Prevnar significantly reduced the risk for otitis media, and as a parent taking my child in to be vaccinated, I'm trying to reconcile the

seven percent reduction with the words "significantly reduce the risk."

DR. BLACK: Okay. You know, "significantly" is a word that has many meanings here, and I guess the statisticians for sure treat that differently than you or I might.

For the individual parent, the effect is not such that it's likely to be noticeable unless the child is one that has frequent or recurrent otitis or goes on to tube placement, in which case, you know, for a family of three or four kids you might expect to notice that.

But on a public health perspective, it is significant. I think as was pointed out, you know, a reduction of a million visits or more per year for otitis media is clearly a significant event as a public health effect, but I think it's fair to say for an individual parent, and it's important that parents realize that the individual parent is not going to notice the difference of an average of .3 otitis media visits over the course of the study, which is what we observed.

CHAIRMAN DAUM: In the strictest sense, you're using the term in the statistical sense, are you not?

DR. BLACK: I think it's to my mind -- I guess it's statistically significant, clearly, and I think from a public health perspective it is as well.

CHAIRMAN DAUM: Thank you.

Dr. Stephens and then Dr. Katz.

DR. STEPHENS: Just to clarify, and I realize the data is meager, but in those failures in the vaccinees, were most of those 19Fs or related serotypes?

DR. BLACK: All of them were 19Fs.

DR. STEPHENS: And what is that number total?

DR. STEPHENS: It's about 20.

CHAIRMAN DAUM: Dr. Katz.

DR. KATZ: These data may have been in the back-up material that I read, but I've forgotten, Steve. Do you have your youngsters broken down who was in day care and who was home dwelling?

DR. BLACK: We have that data from the telephone interviews that were conducted for safety. Day care is not a characteristic that's -- I mean, you can say whether they are -- I guess, rich or poor can change as well, but day care clearly can change. The status can change throughout the trial.

And if we look at the telephone interview data at any point in time, the day care participation rates are similar in the vaccine and control group, but we did not attempt to adjust for that in our analysis since the rates were the same.

We had done a case control study in preparation for this trial that showed that day care was the strongest predictor for risk factor for invasive disease, but that's been done by others as well.

DR. KATZ: But you don't have data to show that

the reduction in the day care population was the same or greater or less than --

DR. BLACK: No, actually we've not looked at that, and I think, you know, with the number cases of invasive -- for otitis, you mean, or for --

DR. KATZ: Yes.

DR. BLACK: No, we have not done that. We'd have to really know what their day care status was at each point in time though. I think it's possible, but difficult.

CHAIRMAN DAUM: I'd like to move on at this point and hear from Dr. Siber, who will give a summary medical impact of Prevnar on AOM, and that will conclude the sponsor's presentation.

DR. SIBER: I'll be very brief and hopefully get us or keep us on time.

I think the main point I want to make about what we've just heard is remarkable consistency of two studies that were done in different countries, in different populations, under different epidemiological circumstances, probably differences in day care use, and so forth, and yet at least qualitatively, if not quantitatively, the results are remarkably consistent.

Overall, vaccine serotype OM had a 57 percent reduction in Finland with a reasonably narrow confidence interval. At Kaiser this was not a primary outcome, and a radically different disease, spontaneously draining ears, showed

a 69 percent reduction in vaccine type isolates from ear tubes.

Only in Finland did we have data on vaccine related serotype OM and the related serotypes also showed a significant reduction at 51 percent with reasonably narrow confidence interval, and there was an increase with non-vaccine serotypes with a negative efficacy, as you've heard, of minus 33 percent.

Nevertheless, that increase was counterbalanced by the positive effects within that efficacy for the vaccine against all pneumococci, 33 percent or 34 percent with, again, a reasonably narrow confidence band.

For recurrent OM, somewhat different definitions. Kaiser and FinOM had similar efficacy, although only the Kaiser study was powered to have significance with regard to the recurrent OM at 12 percent reduction.

All otitis media, again, similar point estimates, but on the Kaiser study it was powered for significance against all otitis media, and with regard to tube placement, and I show here only the follow-up data for the reasons that I think Dr. Kilpi explained as being more relevant to general practice and a higher threshold for placing tubes.

Again, overlapping confidence intervals with 44 and 24 percent respectively, both significant and both with reasonable confidence intervals.

So let me briefly summarize again the health

impact of otitis media and repeat, I think, what's been said before, that one to 1.4 million office visits are prevented each year by Prevnar at the current estimated efficacy rate based on the estimated pneumococcal disease rate or, rather, on the efficacy rate for all otitis media or at least what this is based on. So this is not a trivial public health issue.

We've also heard that there is a measurable decline in antibiotic use that corresponds roughly to the efficacy rate for otitis media, and we would expect in the future perhaps to actually see an impact of that on antibiotic resistance.

And the most important, serious complication of otitis media arguably is ear tube placement, and we calculate an estimated reduction in ear tube placement surgeries of about 60,000 in the United States, extrapolated from Kaiser.

So the otitis media indication, I think, is a rational thing to have as part of this vaccine indication and to be described in the insert. It's now supported by two randomized controlled trials that show statistically significant decreases of OM outcomes, as I've mentioned earlier.

We've seen that there's important medical effects on otitis media disease and its consequences. I think insuring that accurate information is present in the label that informs the significant, but modest effect on otitis media is important so that physicians and parents receive the most accurate possible

information.

Let me make one final point that I think is important with regard to otitis media indication for vaccines. We and other manufacturers have programs directed towards other pathogens, bacterial and viral that cause otitis media, and although such vaccines might have high efficacy against their particular pathogen, they nevertheless, if otitis media itself is used as a standard against which they will be measured, will necessarily have a low overall impact on otitis media because so many pathogens are involved.

So to use a traditional standard of 80 percent, 90 percent efficacy that we used to with vaccines with an outcome like otitis media that is probably microbial would pose, I think a very difficult dilemma for the development of Moraxella catarrhalis or non-typeable Haemophilus or some of the viral pathogens that cause otitis media.

So I would want to ask the committee to consider that in their deliberations about this issue of the low efficacy overall for otitis media, and that's it.

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

Are there committee questions or comments that go toward clarification of the sponsor's presentation?

Ms. Fisher.

MS. FISHER: You said that there is a five percent reduction in antibiotic use in these trials with the use of

Prevnar, correct?

Okay. So you're saying there's going to be an associated decrease in antibiotic use if this indication is forthcoming. Five percent is not a lot, is it, in terms of decrease antibiotic use?

DR. SIBER: In terms of the total number of prescriptions written, it certainly is a large number. Obviously five percent is five percent.

CHAIRMAN DAUM: Okay. Thank you very much.

That, I think, concludes the sponsor's presentation. I thank all of the speakers and committee questions. I think at this moment we're doing very well time-wise. We will take a ten-minute break, 12-minute break and reassemble at 10:35 Eastern time.

(Whereupon, the foregoing matter went off the record at 10:26 a.m. and went back on the record at 10:41 a.m.)

CHAIRMAN DAUM: We will now begin the FDA presentation regarding acute otitis media and Prevnar, and our first speaker will be Douglas Pratt.

DR. PRATT: Good morning. First I'd like to recognize other members of the review team:

Jingyee Kou from Biostatistics;

Marion Gruber from the Division of Vaccine Applications; and

Carl Frasch from the Division of Bacterial Products.

I also see Pam Getson in the audience. She was a biostatistician with FDA to left us recently. She was involved in many of the early discussions on otitis media.

Well, Prevnar was licensed in the U.S. in February of 2000 for prevention of invasive disease caused by the seven pneumococcal serotypes represented in the vaccine. With this supplement to the license application, Wyeth Lederle seeks to extend the approved application to include prevention of otitis media.

Specifically, regulatory approval has been requested to market Prevnar for active immunization of infants and toddlers against invasive disease and otitis media cause by streptococcus pneumonia due to capsular serotypes included in the vaccine.

Some regulatory background is summarized here. VRBPAC met to deliberate approval recommendations for invasive disease in November of 1999, and at that meeting some data relating to acute otitis media were presented.

However, the committee was not asked to consider approval of an indication for otitis media at that time. The license application for acute otitis media was submitted in June of 2000, and following an FDA review, a letter was sent to the sponsor in May of 2001 requesting additional analyses,

clarifications, and other information.

The sponsor responded in October of 2001, and then another FDA letter was sent to the sponsor in March of 2002 after the sponsor had requested that FDA consider additional data from the Finnish follow-up study, which you have seen some of this morning.

And that brings us up to date.

Well, Prevnar is currently the only licensed pneumococcal conjugate vaccine, and Prevnar is recommended for all children under two years of age and for some older children who are at high risk for invasive pneumococcal disease.

Extending the licensed indication to prevention of acute otitis media appears unlikely to impact use of Prevnar in the U.S. in the near future. However, FDA views consideration and discussion of this application by the committee today appropriate for a number of reasons, including those represented here.

Efficacy estimates for acute otitis media outcomes are comparatively low for preventive vaccines. Also, as was mentioned this morning, there's the possibility of increased risk of acute otitis media or negative efficacy for pneumococcal serotypes not included in Prevnar.

And also, concerns have been expressed in the medical community about the potential for unrealistic public expectations. Following the publication of the Finnish otitis

media study by Eskola, et al., a number of letters to the editor regarding that article were submitted to the New England Journal of Medicine, and some of those opinions are paraphrased here.

The overall clinical significance of the treatment effect was questioned. Concerns were expressed about the limited overall benefit. The overall benefit may be misunderstood by the public, and there was concern that the existing recommendations for its use may be compromised.

There was also one letter that incorrectly stated that FDA had rejected use of Prevnar for this indication.

Well, given the global issues and the concerns expressed in the medical community, we thought that an open public discussion of these data and these issues was warranted.

Well, data intended to support the intended indication have been provided from two well controlled clinical trials, the Finnish otitis media trial and the Northern California Kaiser Permanente trial. And some additional efficacy data from extended follow-up from each of these trials has also been provided.

This table reviews some of the important differences between the two studies. The Kaiser study was much larger than the Finnish study. The control vaccines differed. The interval separating new episodes differed, 30 days in the Finnish study, 21 days in the Kaiser study.

And the case definition for the primary endpoint

in the Finnish study was based on bacterial cultures, and in the Kaiser study it was based on automated data searches for AOM visits.

And there were different primary regulatory objectives for these two studies as well.

Also of note, the pre-licensure formulations of Prevnar were abbreviated differently in the two studies. In the Finnish study it was abbreviated PncCRM and in the Kaiser study 7VPnC. In many of the tables that follow those abbreviations will be used, but for the oral presentation, I'll try to refer to the pre-licensure formulation simply as Prevnar.

Well, with that introduction, I'll move on and again review efficacy data from the Finnish study, including supplementary analysis requested by FDA, as well as some of the data from the follow-up study, the Finnish follow-up study, and then go on to discuss efficacy data from the Kaiser study.

Much of this information will be repetitious from the sponsor's presentation. It's the nature of going second in these meetings, but there will be some FDA comments for emphasis on some of the analyses, and for those of you less familiar with the data, this may be helpful.

There will be a brief discussion of safety data that will be limited to clinical trial data from the Finnish study, and then there will be some considerations for the committee to think about in their deliberations before presenting

the questions to the committee.

Primary objective in the Finnish study was to determine protective efficacy of the pneumococcal conjugate vaccines against culture confirmed pneumococcal acute otitis media due to vaccine serotypes.

Secondary objectives were to determine efficacy used in different levels of diagnoses, efficacy in preventing nasopharyngeal carriage, determining the antibody response, as well as the safety and tolerability.

In the Finnish study, subjects were randomized equally to one of three vaccines, Prevnar, PnbcOMP manufactured by Merck, and the Hepatitis B vaccine control.

However, only data related to Prevnar were provided in the application and only data related to Prevnar will be discussed today.

The study was double blind, and eligible subjects were in good health as determined by medical history, exam, and clinical judgment.

Of note, infants born prematurely could be enrolled in the study if they were judged to be in good health.

Children received Prevnar or the control Hepatitis B vaccine at two, four, six, and 12 months of age, and this coincides with the U.S. schedule fir Prevnar. Vaccines administered concurrently with study vaccines were DTP Hib combination vaccines for the first three doses, and these did

contain the whole cell pertussis components.

And then IPV, the second dose of IPV was the only concurrently administered vaccine at the 12 month visit.

Dr. Kilpi talked about case surveillance and ascertainment cases were identified through the study clinics which also provided the well child care. Clinics were open every day of the week, and parents were encouraged to bring their children to the study for respiratory infections or symptoms suggesting acute otitis media.

And if Strep. pneumoniae was found -- excuse me -- myringotomy with aspiration of middle ear fluid for culture was done. If clinical acute otitis media was diagnoses and if Strep. pneumoniae was found, then the serotype was determined, and each child was followed until age two years.

The clinical definition that Dr. Kilpi talked about, it included clinical criteria being a visually abnormal tympanic membrane, suggesting an effusion, and at least one sign of disease, including fever, ear pain, irritability, diarrhea, vomiting, and acute otorrhea or other symptoms of respiratory infections, and this definition appears to be consistent with U.S. clinical practice.

The primary endpoint in the study, as was discussed, was AOM episodes due to vaccine serotypes. There was one secondary endpoint pre-specified. That was first and subsequent AOM episodes due to vaccine serotypes and other

endpoints were pre-specified, including AOM due to vaccine serotypes by dose; all pneumococcal AOM episodes regardless of serotype, and that included culture over PCR; all AOM episodes with middle ear effusion regardless of etiology; and all AOM episodes regardless of etiology, whether or not middle ear fluid was obtained; and then children with recurrent AOM.

The definition of the primary endpoint is that a new episode was considered to start if at least 30 days had elapsed since the beginning of the previous AOM episode due to the same serotype or any interval for different serotypes, and these had to be culture confirmed.

This screen shows graphically a hypothetical example of the counting process for the primary endpoint. Four numbered episodes of vaccine serotypes are shown. Vaccine 19 -- that should be 19F -- accounts for the first and the second episode because they're separated by 30 days.

Vaccine serotype 23 accounts for the third episode, even though 30 days has not elapsed because it was due to a different serotype.

Then a positive PCR, a non-vaccine serotype 6A, and acute otitis media with middle ear effusion, they did not contribute to the primary endpoint.

And then the fourth episode here was due to vaccine serotype 6B.

Well, it's unusual for preventive vaccine studies

that a subject contributes more than one case to the analysis of efficacy. In fact, we could think of no other example of a licensed vaccine for which efficacy was determined using these repeated measures.

A similar analysis was conducted for the primary endpoint in the Kaiser study. The analysis plan was discussed with FDA and did receive FDA concurrence prior to unblinding, but because this statistical approach is somewhat unusual, it's worth describing a little bit, as well as the underlying assumptions.

The analysis used to generalized Cox regression model with Anderson-Gill counting method and risk of acute otitis media was estimated piece-wise, that is, from event to event. The model assumes proportional hazards between groups over time and robust variance estimates were used to compensate for interdependency of events within subjects, and this interdependency was well recognized by all involved. And the analysis is said to provide an average vaccine effect on AOM episodes.

Well, alternatives to these measures would discard some of the data, some or much of the data, but some of these alternative analyses will be shown, will be discussed, and, in fact, FDA looked for multiple checks on the data because of this somewhat unusual approach for a preventive vaccine.

Per protocol follow-up in the Finnish study began two weeks after the third dose. The intent to treat follow-up

began at the time of the first dose.

In general, FDA expects to see intent to treat analyses in addition to protocol analyses, and in most of the tables that follow, both per protocol and intent to treat analyses are shown.

Well, getting into the results, information was collected on demographic variables and some characteristics known to be associated with increased risk of acute otitis media. Despite randomization, some imbalances between treatment groups at study entry were observed after unblinding, and here three selected population characteristics are shown, premature gestational age, low birth weight, and prior acute otitis media episodes at the time of enrollment.

All of these showed a slight imbalance with more -- excuse me. I think this backwards. In any case, there were some imbalances that were noted, and because of the direction of some of the imbalances and the fact that multiple events were counted for individuals, there was a potential that these might influence results, influence the efficacy estimates. So we requested some additional analyses of these endpoints.

Birth weight -- I'm sorry. I wonder if the sponsor can help me right here. These are reversed; is that correct? I think that actually the low gestational age, low birth weight, and prior AOM episodes were actually increased in the Prevnar arm. That's why that they were presented.

Okay. Well, this table shows results of the protocol defined primary analysis AOM episodes due to vaccine serotypes. During protocol follow-up the vaccine efficacy estimate was 57 percent; a lower bound of 44 percent.

The intent to treat estimate was 54 percent, with a lower bound of 41 percent. These estimates were statistically significant, and statistical significance at the five percent level can be inferred here and in the subsequent tables if the 95 percent confidence interval excludes zero. P values will not be shown in most of this presentation.

With a contribution of each of the vaccine serotypes to efficacy as measured by the primary endpoint, as shown here, for intent to treat follow-up the most common vaccine serotypes were 23F, 19F, 6B, and 14. Statistical significance was demonstrated for the individual serotype 6B, 14, 18C, and 23F.

The lowest efficacy estimate was for serotype 19F, ten percent, and the intent to treat analysis, but this was not statistically significant.

There were few episodes for serotype four or 9V.

The protocol defined secondary endpoint examined first and subsequent episodes of AOM due to vaccine serotypes. This analysis would count only one -- excuse me -- the first episode analysis would count only one episode per subject and take into account time to first event.

Efficacy estimate for prevention of first episode was 52 percent in protocol, 45 percent in the intent to treat analyses, and these were statistically significant.

Subsequent episodes were also statistically significant, 45 percent per protocol, 49 percent in the intent to treat.

It's also clear from this slide that most of the episodes were first episodes comparing, say, for the Hepatitis B group 177 to 73 or 89 to 18. Most of the episodes were, in fact, first episodes.

The efficacy estimate for culture confirmed to pneumococcal AOM, regardless of serotype, was 34 percent in the protocol analysis, and this was statistically significant. Results of intent to treat analysis were similar.

Although not specified in the protocol as the primary or secondary endpoint, FDA viewed this endpoint as very important in addressing the clinical significance of the vaccine in preventing otitis media.

Analysis of pneumococcal AOM as determined by PCR was specified in the analysis plan. However, the PCR data was not available at the time the amendment was submitted. These data were submitted on FDA request during the review period.

I'll go ahead and talk about some of the exploratory endpoints here. The efficacy for prevention of pneumococcal serotypes belonging to the same sero groups taken

collectively was also statistically significant, 51 percent in the protocol analysis, 44 in the intent to treat, both statistically significant.

And when examined by the individual serotypes, serotype 6A, although not a vaccine serotype was associated with a substantial number of cases and, in fact, was statistically significant.

As was mentioned earlier, serotype 19A, related to the vaccine serotype 19F, actually had a slightly higher efficacy estimate, 21 percent, than was observed for 19F.

These are intent to treat analyses. I think this morning the sponsor showed the protocol analyses for these serotypes.

Again, looking at other than vaccine related serotypes, there was a negative vaccine efficacy estimate, minus 34 percent in the protocol, minus 39 percent in the intent to treat. For protocol this was borderline statistically significant, and the intent to treat, in fact, was statistically significant.

Thus, subjects vaccinated with Prevnar were actually at increased risk of getting AOM due to one of the vaccine unrelated pneumococcal serotypes. The most common unrelated serotypes belong to serogroups three, 11, 15, and 35. If this effect were to occur with widespread vaccine use, one might expect to observe replacement vaccine serotypes with non-

vaccine serotypes in the general population as causes of otitis media.

Recurrent otitis media was defined as three episodes within six months or four episodes within 12 months. AOM episodes for this endpoint were due to any cause, whether pneumococcal or not.

The efficacy estimate here in the per protocol analysis was 16 percent. It was nine in the intent to treat analyses. Neither of these were statistically significant. However, demonstration of efficacy for this endpoint was not a primary objective, and the study was not powered to demonstrate efficacy for that endpoint.

Other planned analyses included AOM with middle ear effusion and all cause AOM regardless of etiology.

The efficacy estimate for AOM regardless of etiology was six percent in the per protocol analysis, four percent in the intent to treat analyses. Neither of these were statistically significant, but again, the studies were not powered for these outcomes.

It is noteworthy that the six percent estimate is actually quite close to the estimate that was obtained in the Kaiser study for a similar outcome.

Well, nasopharyngeal carriage was assessed as a secondary objective at two time points in the Finnish study, at 12 months and at 18 months. At 12 months the carriage rate of

vaccine serotypes was reduced 17 percent. That difference was not statistically significant.

However, at 18 months carriage was reduced 41 percent, and that estimate was statistically significant. But for this table relative risk estimates are shown rather than difference estimates, which were in the application and the study report and also in the briefing document. This is to be more consistent with the other efficacy analyses that have been shown.

Of note, the sponsor has not proposed including efficacy data for carriage in the label with this amendment.

A serology cohort was comprised of 115 children enrolled at one center. The serology cohort for the two treatment groups appear to be well balanced for demographic characteristics. The geometric mean concentration serum antibody to type specific pneumococcal polysaccharides as determined by ELISA are summarized here on this screen. Confidence intervals are omitted for simplicity of presentation.

As can be seen, there's substantial increases in antibody concentrations over control were observed for each type and then going from the third dose to the fourth dose for Prevnar, increases were seen for each of the seven types.

This screen shows serotype specific efficacy estimates from the primary analysis along with the GMCs that were just shown. It's worth noting that although efficacy estimate for serotype 19F was the lowest of the seven serotypes, 25

percent of the per protocol analysis antibody responses were actually comparable to the other serotypes, both after dose three and after dose four.

The highest efficacy estimate was for serotype 6B. However, that had one of the lowest ELISA GMCs after the third dose, though it appeared to have a good boosting response for the fourth dose.

So it appears that antibody levels as determined by ELISA do not appear to provide any insight regarding efficacy by serotype.

There were a few cases of invasive disease due to pneumococcus in the Finnish study. I compiled this table of the four episodes. There was only one in the Prevnar group. This was due to a type not included in the vaccine.

There were two vaccine serotypes, 23F and 19F, in the Hepatitis B control arm.

I'll now discuss some issues that were identified during the review and present some supplementary analyses that were conducted upon FDA request.

As noted earlier, despite randomization there were some imbalances between treatment groups with respect to certain risk factors for otitis media that were observed after unblinding.

To determine whether the imperfect distribution of these risk factors between the two groups would have a major

effect on efficacy estimates, covariate adjusted analyses were performed by the sponsor on FDA request.

The supplementary analysis was not part of the pre-unblinding analysis plan. So the effect of gender, AOM history prior to enrollment, and day care attendance on the number of AOM episodes was, in fact, highly significant. However, the interaction between these variables and the vaccine effect was not.

Similarly, no significant interactions were seen between vaccine effect and gestational age, birth weight, breast feeding, or household smoking. And as shown in this table here, all of the adjusted efficacy estimates were similar to the unadjusted estimates. Fifty-four percent, this is the intent to treat analysis. Whether adjusted, they were 54 percent unadjusted, 54 percent, 32 percent, the same.

Actually the adjusted estimate regardless of etiology actually went up a little bit. So these analyses were reassuring in that the observed imbalances for known risk factors were unlikely to affect the outcomes.

Well, it was apparent from examining the culture results from individual subjects that some subjects contributed multiple episodes of the same serotype to the analysis. This screen shows an example of subjects from the control group for whom serotype 23F was isolated on multiple occasions extending over nearly a year.

This subject actually contributed four cases or four episodes to the analysis of the primary endpoint, as the first three episodes here were all within the 30-day window and collectively accounted for one episode.

Here's another example from the Prevnar group, actually two examples. Subject 1450 contributed three episodes of 23F, the vaccine serotype, to the vaccine serotype analysis, and the non-vaccine serotype 15 for subject 2241 contributed three episodes to the analysis of all pneumococcal regardless of serotype.

Well, to assess the effects of these counting multiple episodes per subject on the analysis of the primary endpoint, FDA requested supplementary analyses in which each serotype could be counted no more than once per subject.

This table shows the supplementary analysis for the primary endpoint conducted after unblinding as requested by FDA. The efficacy estimate determined after exclusion of subsequent episodes was 55 percent in the per protocol analysis versus 57 percent in the original analysis plan. The confidence intervals also remained fairly narrow.

So excluding subsequent episodes due to the same serotype from the analysis did not appear to affect the efficacy estimate substantially, and this provided a check, if you will, on the analysis of recurrent events.

Well, a similar analysis was conducted for the

endpoint of all AOM episodes due to pneumococcus regardless of serotype, again, excluding the same episode if it occurred more than once in a subject, and here, again, the efficacy estimates were identical, 34 percent, in the per protocol analyses with nearly identical confidence intervals as well.

So, again, these were reassuring with respect to the effect of multiple counting.

Analyses using a case definition based on identification of pneumococci by PCR was specified in the study protocol, but these were not available at the time the study report was written and were not provided with the application.

These were provided during the review period on FDA request.

The PCR assay detects the pneumolysin gene, a gene common to all Strep. pneumo., but it does not distinguish among the serotypes.

In the per protocol analysis of efficacy based on PCR the efficacy estimates were somewhat lower, 20 percent per protocol versus 34 percent, 18 percent intent to treat versus 32 percent by culture, and the efficacy estimates were quite wide.

PCR confirmation contributed actually to a substantial number of new cases. Compare per protocol of Hepatitis B, 414 by culture, 678 by PCR. We saw analyses this morning looking at quantitative PCR. Those data were not in the submission. We had not seen those data before. I think they're

interesting. We really can't comment on those data.

But in any case, although the efficacy estimates were lower by PCR, they remain statistically significant.

The clinical significance of the positive PCR and the culture negative is not clear at this time.

A question was asked about antibiotic use this morning, and in fact, we had the same question. Antibiotic usage was not included among the prospectively defined study outcomes, and no analyses were provided with the application.

However, data was recorded on the case report forms during the course of the study. Clearly patterns of antibiotic use could impact on the acute otitis media outcomes.

If use of prophylactic antibiotics were significantly greater in the Prevnar group than in the control group, then some of the apparent treatment effect might be due to the prophylactic antibiotics. So in any case, FDA requested that these data be compiled and analyzed and submitted.

And as shown, the number of subjects receiving antibiotics for treatment was less in the Prevnar group, and this approach reached statistical significance at the .05 level.

The number of subjects receiving antibiotics for prophylaxis and regardless of purpose were also nominally smaller in the Prevnar group.

Taken together, these data relating to antibiotic use during the Finnish study are consistent with a vaccine effect

in prevention of acute otitis media.

Information about tympanostomy tube placement during the Finnish study was recorded on the case report forms as well. During the course of the study, these data were not with the initial applications. FDA requested that these data be provided to examine consistency of effect with the Kaiser study for first tympanostomy tube placement.

And we also got information that the recommendations regarding ear tube placement in Finland were similar to U.S. practice.

As shown here, actually the rates of first ear tube placement, number of subjects with events in this table were quite similar and no efficacy estimate was provided. It was suggested that because of the close follow-up during the study that subjects actually sought treatment with ear tubes more often than would ordinarily be the case in Finland, and these rates actually were higher, I think, tenfold higher, nearly tenfold higher than common practice in Finland and also much higher than practice in the Kaiser system.

Well, subsequently long-term follow-up data from the Finnish study became available, and in February of 2002, the sponsor proposed an analysis plan of these follow-up data with inclusion to the licensed application.

In the follow-up study, all eligible children were now four to five years of age at the planned follow-up visit.

Parents and investigators were unblinded to treatment assignments at this time.

Now, two populations were evaluated, and the first population included volunteers to the follow-up study. They participated in parental interview for otitis media history, an ear exam, and then records of procedures were verified through the hospital or private physician's records.

The primary analysis of the follow-up data was based on this volunteer population. Then a secondary analysis was performed on the original cohort that remained available for follow-up in the area.

In these analyses, in contrast to what was seen in Kaiser, this is all tympanostomy tube placement, not just the first event.

So in the primary analysis after this follow-up cohort, a total of 756 or about 46 percent of the original 1,662 randomized children enrolled and completed the assessments. The efficacy estimate for ear tube placement for this population during the efficacy study was 12 percent, and this was now statistically significant. That is the efficacy for the period two months to two years during the original trial.

And in the long-term follow-up from two years to four to five years of age, the efficacy estimate was 39 percent. This was statistically significant, though with fairly wide confidence intervals.

In evaluating this result, I think it's important to note that this was a self-selected subgroup of volunteers. Enrollment was not even between the two groups, 353 versus 403.

Also, these children were more otitis prone than the entire study population. That's not easy to see, but the rates were actually increased in this population over the larger cohort. And then, again, the follow-up was not blinded.

It's questionable whether these data actually qualify as an adequate and well controlled trial by the regulatory definition. However, I think they can be viewed as supportive for the other study, for looking at consistency on the ear tube placement effect.

Well, this is the results of the secondary analysis from the follow-up study. Again, here all records were confirmed by checking the hospital records. There was no volunteerism involved here. Everyone that was available that was followed.

Again, this population, during the study itself, two months to two years' follow-up. The efficacy estimate was four percent. That was not statistically significant, but the long-term follow-up, two years to five years, estimate was 44 percent, and this was statistically significant.

I'll move on now and go over the Northern California Kaiser Permanente otitis media efficacy results. I'll go quickly over much of this that has been discussed this

morning, and it's probably fairly clear to everyone now.

The study was randomized and double blind. The control vaccine was an investigational meningococcal C conjugate vaccine. Evaluation of AOM was actually a secondary objective, as was discussed this morning. There was no standardized clinical case definition, and tympanocentesis and routine culture of middle ear fluid was not done. Rather, cases were identified through automated database searches to identify the diagnoses.

A diagnosis was based on routine clinical practice using a check-off box on the patient encounter form. An AOM episode, a new episode began if at least 21 days had elapsed. This is somewhat shorter than in the Finnish study. And frequent acute otitis media was defined as three AOM episodes within six months or four episodes within 12 months.

The primary objective was looking at reduction in all AOM episodes. Secondary outcomes that were pre-specified included first episode, frequent AOM, first tympanostomy tube, all AOM clinic visits, and ruptured eardrums.

The primary endpoint is summarized here. Again, per protocol, overall reduction in AOM episodes was seven percent per protocol, and in the intent to treat was 6.4 percent.

The intent to treat analysis here actually includes substantially more subjects. You can see from 16,000 to 25,000, and the reason for that is that there was differential follow-up. Not all of the subjects had received the full three

doses at the time that the study code was unbroken.

This is one of the secondary analyses, risk of first episode or at least one episode. Due to the shorter, 21-day interval between new episodes in the Kaiser study, it's possible that some over counting might occur if some episodes were slow to resolve.

Also, using the patient encounter form, a follow-up visit might not be easily distinguished from a visit for a new episode.

Well, one check on the possibility that the definition used might over count or otherwise inflate the outcome would be to look at one episode per subject, and that is captured in this analysis. Here the per protocol analysis of first episode, reduction was 5.4 percent, and in the intent to treat, it was 4.9 percent. Both of these were statistically significant.

For the analysis of frequent acute otitis media, that vaccine efficacy estimates in preventing frequent were 9.5 percent in the per protocol analysis, 9.2 percent in the intent to treat analysis, and these were also statistically significant.

First, tympanostomy tube placement, again reduced in the per protocol analysis by 20 percent, intent to treat analysis by 21 percent. These confidence intervals are fairly wide. Nevertheless, the results were statistically significant.

Thirteen ruptured eardrums, culture positive for

vaccine serotypes were observed during per protocol follow-up, four in the Prevnar group, nine in the control group. The efficacy estimate was 56 percent and 57 percent in the intent to treat analyses. Neither of these were statistically significant.

When looking at all pneumococcal serotypes, per protocol estimates for reduction was 62 percent, not significant, but for intent to treat, 61 percent was statistically significant.

Well, vaccine serotype 19F and related serotype 19A accounted for all of the serotypes from the ruptured eardrums in the Prevnar group, and 39 percent of those from the control group.

Taken together, vaccine serotypes accounted for 20 out of the 25 isolates or 80 percent of all of the isolates from ruptured eardrums, all of the pneumococcal isolates.

Extended follow-up data for acute otitis media accumulated after breaking the treatment codes for about another year before parents and clinicians were informed of the treatment assignments and Prevnar was offered to the control group.

This table compares the efficacy estimates at the time of the primary analysis for data where the database was closed on April 30th, 1998, and then the additional follow-up data to April of '99.

All of the efficacy estimates were similar, and the confidence intervals actually became more narrow for many of

the outcomes.

I'll now talk a little bit about safety data from the Finnish otitis media study. The Finnish study does contribute new controlled safety data to the safety database for Prevnar. These data were reviewed in the otitis media amendment, and the briefing document contains a more full discussion of the safety data.

The relevance and usefulness of these data to the U.S. population are somewhat limited because, for one reason, the wholesale pertussis containing DTaP Hib combination was administered with the first three doses rather than DTaP vaccine, which is common practice in the U.S. now, and this can complicate some of the assessments of systematic reactions.

Also, the Finnish population does not reflect the heterogeneity of the U.S. population, and also the study was really not large enough to detect uncommon adverse events.

However, parent compliance with report of vaccine reactions was nearly complete in the Finnish study, and so reported data are probably reliable. And these data do confirm an incremental increased risk of fever after each of the three doses, low grade fever after each of the first three doses and also an increased risk in higher grade fever after the third dose.

However, the frequency of high grade fever never exceeded two percent for any of the doses. Also, increased

crying was observed after each of the three doses.

This table shows data after the fourth dose. Here the concurrent immunization was the second dose of IPV. Again, low grade fever was statistically more frequent. High grade fever, there was no difference.

So overall the safety data from the Finnish otitis media are consistent with earlier observations regarding the safety of Prevnar. As had been previously observed, Prevnar was associated with increased fever, increased low grade fever, but complications of fever were uncommon.

In fact, there were no febrile seizures temporally associated with administration of either vaccine in this study.

The committee will not be asked to comment on safety at this meeting today. Prevnar is now in wide use. Large post licensure safety studies are underway.

Vaccine labels can be updated at any time with important safety information, and information from the ongoing post marketing study conducted at Kaiser identifying any new safety concerns that better quantify known or suspected adverse events, the label will be updated accordingly.

Well, before presenting the questions, I'd like to show a few screens with things for the committee to consider in their deliberations. First, there really is no guidance from regulations or other published documents which specifically address the minimum level of efficacy required for licensure of a