U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL

PRODUCTS ADVISORY COMMITTEE MEETING

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Friday, November 5, 1999

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The meeting took place in Versailles Rooms I and II, Holiday Inn, Bethesda, MD, at 9:00 a.m., Harry B. Greenberg, M.D., Chair, presiding.

PRESENT:

HARRY B. GREENBERG, M.D., Chair
NANCY CHERRY, Executive Secretary
ALICE S. HUANG, Ph.D., Member
MARY K. ESTES, Ph.D., Member
ROBERT S. DAUM, M.D., Member
KWANG SIK KIM, M.D., Member
DAVID S. STEPHENS, M.D., Member
DIXIE E. SNIDER, JR., M.D., M.P.H., Member
BARBARA LOE FISHER, Member
MARY GLODE, M.D., Invited Participant
ALISON O'BRIEN, Ph.D., Invited Participant
L. PATRICIA FERRIERI, M.D., Invited Participant
PAMELA HARTIGAN, Ph.D., Invited Participant
MARTIN MYERS, M.D., Invited Participant
KAREN GOLDENTHAL, M.D., FDA Representative

PRESENT: (CONT.)

DR. DOUGLAS PRATT, FDA Representative
DR. CARL FRASCH, FDA Representative
DR. LYDIA FALK, FDA Representative
GEORGE SIBER, M.D.C.M., Sponsor Representative
JILL HACKELL, M.D., Sponsor Representative
STEVE BLACK, M.D., Sponsor Representative
DR. TERHI KILPI, Speaker
JOHN BARTHELOW CLASSEN, M.D., Public Commenter
CARLA NEWBY, Public Commenter

A-G-E-N-D-A

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

(9 00 a.m.)

CHAIR GREENBERG: If people could start getting into their seats. People, please take your seats.

Well, good morning, everybody. I'd like to welcome you to the open session on Friday, November 5th, of the VRBPAC Committee Meeting, and to start off we have a few administrative announcements.

EXECUTIVE SECRETARY CHERRY: Good morning, everyone, and welcome.

Yesterday, I announced that some of our committee members could not be here. I neglected to mention that Doctor Faggett could not join us at the committee table. It also looks like Doctor Finkelstein won't be able to, and also on your roster you may see that we had intended to bring in Doctor Butler, he's unable to be with us today.

I have a short conflict of interest statement to read. The Director of the Center for Biologics Evaluation and Research has appointed Doctors Butler, Ferrieri, Glode, Hartigan and O'Brien as temporary voting members. The following announcement addresses conflict of interest issues associated with the session of the Vaccines and

Related Biological Products Advisory Committee on November 5, 1999, for the committee discussions on safety and efficacy of pneumococcal 7-valent conjugate vaccine for prevention of invasive disease.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the meeting participants. In accordance with 18 USC 208, Doctor Robert Daum has been granted a waiver which permits him to participate in committee discussions. In accordance with the Food and Drug Administration Modernization Act of 1997, Section 505, Doctor Patricia Ferrieri has been granted a waiver which allows her to participate fully in the committee discussions. Doctor Kathryn Edwards has recused herself from this discussion. Doctor Estes disclosed a potential conflict of interest which was deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest. A written appearance determinationunder Section 2635.502 of the Standards of Ethical Conduct has been granted to permit her to participate in the committee discussions.

In the event that discussions involve specific products or firms not on the agenda, and for

which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussion. Their recusals 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 address any current or previous involvement with any firm whose products you wish to comment on.

Copies of all waivers and appearance determinations addressed in this announcement are available by written request under the Freedom of Information Act.

CHAIR GREENBERG: Thank you, Nancy.

I'd just like to make a brief announcement. It's my intention when we get to lunch to hold a very, very brief lunch break of 15 minutes. I apologize to people in the audience, most of you are probably, unlike me, unable to eat in a minute or two, but we have a number of committee members who have planes to catch and I'm trying to keep everybody here for a very important meeting as long as possible. So, whenever the morning session ends, there will be a brief 15-minute break, eat as fast as you can and get back here.

And, without further ado, I'll start with, again, I want to admonish all speakers, you'll get your time but no more, so be crisp and timely, and we'll start with Doctor Carl Frasch.

DOCTOR FRASCH: Okay. I would like to introduce the session. As you all know, we are talking about the Wyeth-Lederle application for their pneumococcal 7-valent conjugate vaccine, diphtheria CRM protein. This application was received as a rolling submission, and the official receipt date was June 1, 1999. What we mean by rolling submission, we got the first parts for review, I think it was toward the end of February, and then the final submission was received — was dated May 31, and received June 1.

Now, CBER agreed with the company that the application would be given priority review for invasive disease. I would like to point out that while we have over ten years of experience with another conjugate vaccine, the Hib conjugate, the pneumococcal conjugate represents a major increase in complexity for the manufacturing process, for clinical evaluation of seven different immune responses simultaneously. This vaccine is a first multivalent conjugate vaccine, and it's the first pneumococcal conjugate vaccine, and the indication being sought

today is for invasive disease in infants and young children.

The pneumococcus causes a spectrum of clinical diseases, including pneumonia, with or without bacteremia, bacteremia, meningitis and acute otitis media. Again, today we are going to focus upon the bacteremia and meningitis, which are the two primary invasive disease endpoints.

As you know, a high level of efficacy against invasive pneumococcal disease was found and has been reported at ICAAC and other meetings. Thus, we will focus in the CBER presentation more upon the vaccine safety, the immunological consistency, efficacy lots versus manufacturing lots, manufacturing consistency, physical and chemical testing. This part we've already heard a little bit about. And, for the CBER, Doctor Douglas Pratt will represent a review of safety, efficacy and immunogenicity, and then he will conclude the formal presentations today with a brief summary and questions for the committee members to consider.

Thank you.

CHAIR GREENBERG: Thank you, Carl.

I neglected to ask my colleagues to introduce themselves, so before we start with the

manufacturer I'd just like to go around the table and in my haste to move this along I neglected all of you.

Doctor Daum.

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

DOCTOR KIM: Kwang Sik Kim from Children's Hospital Los Angeles.

DOCTOR SNIDER: Dixie Snider, Associate Director for Science, Centers for Disease Control and Prevention.

DOCTOR HUANG: Alice Huang from the California Institute of Technology.

DOCTOR STEPHENS: David Stephens, Emory University.

DOCTOR FISHER: Barbara Loe Fisher, National Vaccine Information Center.

DOCTOR ESTES: Mary Estes, Baylor College of Medicine, Houston, Texas.

DOCTOR HARTIGAN: Pamela Hartigan with the V.A. Cooperative Studies Program at Yale University.

CHAIRGREENBERG: Harry Greenberg, Standard University and the Palo Alto V.A. Medical Center.

DOCTOR FERRIERI: Patricia Ferrieri, University of Minnesota Medical School, Minneapolis.

DOCTOR GLODE: Mimi Glode, University of

Colorado, Denver.

DOCTOR O'BRIEN: Alison O'Brien, Uniform Services, University of the Health Sciences, Bethesda.

DOCTOR MYERS: Martin Myers, National Vaccine Program Office.

DOCTOR GOLDENTHAL: Karen Goldenthal, FDA.

DOCTOR PRATT: Douglas Pratt, FDA.

DOCTOR FRASCH: Carl Frasch, FDA.

CHAIR GREENBERG: Thank you.

If the sponsors -- my line of sight is blocked.

DOCTOR FALK: I'm Lydia Falk, FDA.

DOCTOR SIBER: Good morning. My name is George Siber, I have no formal relationship with the agency with the homonymous name.

It's my pleasure this morning to introduce the Wyeth-Lederle Vaccine's presentation on the 7-valent pneumococcal conjugate vaccine, which is trade named Prevenar.

In the next hour and a quarter we will present four talks. I will briefly discuss the rationale for pneumococcal conjugate vaccine and its design. Jill Hackell will discuss immunogenicity and reactogenicity of the pneumococcal vaccine. Phase III trial in northern California will be discussed by

Steve Black, and he and Henry Shinefield are the co-investigators of this trial, and I will conclude briefly with the potential public health impact of Prevenar.

Later, after lunch, Doctor Terhi Kilpi of the KTL will discuss the thin-arm trial of otitis media in Finland briefly, the preliminary results.

To begin with then, the clinical manifestations of pneumococcal disease, the pneumococcus is the single most important bacterial pathogen of children. This pie diagram shows you that it is a major cause of meningitis, bacteremia and sepsis, of pneumonia, and of otitis media and probably sinusitis as well.

Meningitis is a very severe, although somewhat rare, disease in all ages. It's estimated that each year there are 3,000 cases per year in the U.S., about half of which occur in children under five. There are neurological sequelae, especially sensory motor and hearing loss, in up to 50 percent of the cases, and there is up to a ten percent mortality from meningitis.

This shows you the cerebrum of a patient who died from meningitis, and it's not hard to imagine why there is substantial potential for neurologic

damage when there is a purulent exudation over the cerebral convolutions like this.

Bacteremia is more common, 61,000 overall with about one quarter of these occurring in children under five years of age, typically occult, but the fear with bacteremia is that there will be seeding of the bacteria to various sites in the body, systemic sites, as I mentioned meningitis, as well as other areas of the central nervous system, epidural empyema, that's puss around the lining of the brain, and brain abscess. There can also be rarely seeding of the heart, because purulent pericarditis, as well as the heart valves endocarditis, seeding of the peritoneum with peritonitis. In addition, the skin, soft tissue, the bone, and the joints can be seeded by the pneumococcus.

Pneumonia, more common, we have 5,000 estimated pneumonias in the U.S. in all ages, and about one sixth of these are children under five years of age. As was already mentioned, typically, the pneumonias are not bacteremic and so they are difficult to diagnose.

Pneumococcal pneumonia can be extremely severe. This shows a child with lobar pneumonia and empyema, which means puss around the lining of the

lung. This can be complicated also by lung abscesses, requiring drainage and surgery.

Overall globally, pneumonia is actually one of the major killers, if not the major killer, of children. WHO estimates that 4 million children each year die of acute lower respiratory disease, and that of these about a third, or 1.2 million children, die of pneumococcal pneumonia.

Finally, otitis media, an enormous burden of disease with otitis media, 7 million cases per year estimated by CDC, of which the majority, over 5 million, are children. Complications include with recurrent otitis media, or especially severe otitis, chronic otitis, hearing loss, cognitive development problems, there may be a need to insert PE tubes, ear tubes. This is the single, most common procedure of children that requires a surgical procedure that requires general anesthesia.

Another public health issue is that a lot of antibiotics are used because one is worried about pneumococcal disease, and that, as you all know, has led to emergence of antibiotic resistance in the pneumococcus and many other organisms as well.

This shows you an angry, red, bulging eardrum, typical of severe purulent otitis media with

the pneumococcus, and an occasional complication is mastoiditis, with a bulging area behind the ear. In this case, a drainage tube has been placed to facilitate drainage of puss from the mastoid cavities.

Now moving on to epidemiology. The age distribution is shown here, and really resembles very closely the age distribution that we had with haemophilus influenzae b, both in the shape of the curve and in its magnitude, with peak age of pneumococcal disease occurring between six months and 18 months of age.

Orin Levine, at CDC, and colleagues around the country, have performed recently a risk factor analysis for pneumococcal invasive disease, and a striking finding that is true for all age groups through six years is a two to three-fold increased relative risk if you are intending daycare, and that risk is especially high in the first year after entry into the daycare. In the very young children, breast feeding appears to be quite protective, .27 relative risk. And, in the older children having had a recent course of antibiotics is associated with a 2.4 fold increased risk and in 24 to 59 months old a two-fold relative risk for crowding conditions.

Different ethnic groups have different

risks. This again shows you age specific rates. Whites are shown in black at the bottom. What you can see is that African Americans have a five to ten-fold higher risk throughout all these age groups through six years of age invasive pneumococcal disease. And, similarly, Alaska natives and American Indians could also be plotted here, five to ten-fold higher risk. And, a very high-risk population are patients with sickle cell disease who have functional asplenia with a 50 to 100-fold higher risk again of having pneumococcal invasive disease, frequently very severe and fulminant.

Other conditions that predispose pneumococcal disease or a severe disease often are asplenia, various acquiredgenitalimmunodeficiencies, particularly, HIV, cancer, cancer chemotherapy, bone marrow transplantation, and, chronic diseases, kidney, liver, lung and heart.

Now, this shows the pneumococcus, and in particular what I want to emphasize is that this gram positive organism is coated by a capsule, a carbohydrate capsule, which serves a very important function for the organism. It is not susceptible to antibody and complement lysis, it has to be opsonised for phagocytosis, and the capsule is an antiphagocytic

structure, phagocytes don't like to eat it unless it is covered by antibody and complement. And so, the real focus of most vaccine development has been the capsule.

The problem has been that there are more than 90 serotypes of pneumococcus which fall within 45 serogroups. There is no immunologic cross reactivity between these 45 serogroups. There is some cross reactivity within some of the types within the serogroups, and recent evidence we have suggests also some cross protection.

Although these serotypes and serogroups vary by geography and over time, fortunately, a relatively small number of the 90 or 45 count for the majority of illness, both in the U.S. and elsewhere in the world.

In thinking initially about the U.S. formulation, we basically looked at serotype distribution of pneumococcus in the U.S., in young children, and this shows you an Austrio-Hausdorffogram which gives you types, 14 being the most common, down to 9b, so the top seven types, as you can see cumulatively, accounted for about 80 percent of all pneumococcal invasive disease in young children — if we see cross protection with the cross reactive type,

that adds another eight percent or so to have almost go percent coverage of all pneumococci with the current 7-valent formulation.

This formulation would cover 88 percent of bacteremias, 82 percent of meningitis, and a somewhat lower percent, 71 percent, of otitis media.

Emergence of antibiotic resistance is one of the other reasons why a pneumococcal vaccine would be of substantial interest. As I mentioned with the antibiotic use over time, there has been increased rates of pneumococcal resistance to penicillin intermediate or high-level resistance, and this has been a concern both for the medical community and for the public, because we fear that soon we may not have effective antibiotics against these serious infections.

This shows you actually the rise in resistance in the U.S., from five percent in 1988 to 32 percent in 1998, and of interest is that almost all the resistant strains fall into type six — or groups six, 14, 19, 23 and nine, and you should note that all of these types are in the 7-valent formulation.

Conjugate vaccine design and development, we have a pneumococcal vaccine already, it's the 23-valent polysaccharide vaccine, which has had

tremendous value because it works well immunogenic in older children and adults, and it's very clearly effective against bacteremic disease, it is effective against pneumonia in young adults, as shown in south Africa. There does remain controversy about how effective it is against pneumonia in the elderly.

But, a limitation of the polysaccharide vaccine is that it does activate T-cells, and nor does it prime for an anamnestic or memory response to subsequent exposure to polysaccharide. In addition, infants do not respond to many of the polysaccharide serotypes, and for this reason this vaccine is not indicated in children under two years of age. And, even older children often have somewhat lower and short-lived antibody responses compared to adults.

So, the solution to this problem was really that one couples the polysaccharide, shown here as graphically in white, to a protein molecule shown in green, a covalent coupling methodology, and when one does this the immune system sees this in a way that the T-cells that have polysaccharide antibody on their surface can enlist the help of T-cells by virtue of carrier epitopes, to get help to proliferate, differentiate and to produce larger amounts of anti-polysaccharide antibody and high quality, high

affinity anti-polysaccharide antibody.

The best demonstration of the power of glyco conjugate vaccines is the Hib vaccine. This shows U.S. data, what happened with the introduction of Hib vaccine in late '89, and this is Hib invasive disease declining to essentially — extremely low levels, let's put it that way, currently. Also of interest on this slide is that non type b disease shown here really did not increase to replace that niche.

The other expectation of glyco conjugate vaccine, in particular Prevenar, is that we expect this to be a safe vaccine, and the reason is that the two components of Prevenar have had extensive safety experience individually. Hib TITER, which is Hib polysaccharide coupled to the CRM_{197} protein by reductive amination contains the same carrier protein, CRM, and the same linkage chemistry as we have with Prevenar. 129 million doses of Hib TITER are estimated have been distributed safely since its approval in 1989.

Thepneumococcalpolysaccharidevaccine is made by several manufacturers also have had extensive experience, albeit in children over two years of age, and about 55 million of doses of those polysaccharides

have been distributed safely since 1983, and the seven types that are in the conjugate vaccine are also contained in the 23-valent formulation.

Now, inmakingthe polysaccharide, I think it's been said already that this is a very complex vaccine, and arguably the most complex vaccine that has ever been developed, and the reason for that is that there are seven distinct capsules that are purified, these are the organisms with the capsules around them. These organisms are fermented and then the capsule is purified to high levels of purity, each individually shown here, and then each capsule is activated separately, conjugated separately to the CRM carrier protein to create seven separate conjugates, and then these seven conjugates are mixed together and formulated into the final vaccine.

In addition, there are quality control tests at multiple stages during the production process to ensure that we have total control over the production process and get consistent manufacture.

The final formulation contains two micrograms of each of six types, and four micrograms, as was previously mentioned, of type 6b to ensure the immunogenicity of the least immunogenic of types.

Notice that the total carrier dose of CRM

is 20 micrograms, which is similar to the carrier dose in Hib TITER, and the adjuvant is aluminum phosphate, .5 milligrams, and there is no preservative in Prevenar.

Finally, the scope of the Wyeth clinical program, we have done a series of studies which will be described by Jill Hackell that look at polysaccharide size and linker initially to choose the optimal size and linker, also the dose response, and we also show the polysaccharide challenge results in an excellent immune response in primed individuals.

We looked at immunogenicity in infants and concomitant vaccines in a number of studies. The Phase III efficacy trial was done in Kaiser, which we'll hear about from Steve Black, lot consistency and bridging studies were performed and were successful.

Additionally, a series of studies have been done in various ages of catch-up cohorts, and again, you'll hear more about that one. So, all tolled, this submission to FDA covers 20,000 infants, 54,000 doses, as well as booster doses in more than 10,000 infants, in older children, 700 infants and 1,100 doses.

In addition, and I don't have time to go into this, a large number of studies have been done

with investigators externally listed here. This reads like a Who's Who of Bacterial Vaccine Investigators, and in particular I want to mention that NIH, NIAID, has supported this program for more than a decade, perhaps, 15 years, and in particular I want to mention the Program Officer, David Klein, Pam McInness, George Corlin and John LaMontagne, who have been strong supporters throughout the development effort for pneumococcal conjugate vaccine.

These studies have covered a variety of high-risk populations that are shown here, and in addition there are three Phase III trials, one just completed in Finland, as well as a trial in Native Americans by Mathu Santosham, and one in South African infants by Keith Klugman that are underway.

All tolled at this time, 16,000 additional infants have been immunized under these programs, which are not part of the submission, for a total of about 46,000 — 36,000 in total.

We propose to you that the data we have collected supports a routine infant immunization schedule in two, four, six and 12 to 15 months, as well as we have regimens that we will propose for unvaccinated children over six months of age, which range from one to three doses depending on the age

group.

So, with that, I'd like to introduce Jill Hackell, who will now cover the immunogenicity and reactogenicity of pneumococcal conjugate vaccine.

DOCTOR HACKELL: Thank you, George, and good morning everybody. I have a lot of data to present in a very short time, so I'm going to get right into it.

I'm going to start with a series of studies on the immunogenicity of this vaccine. And, I'm going to cover four broad topics. First of all, you'll see the kinetics of the antibody response in children who received the pneumococcal vaccine in the routine infant schedule. Next, I will cover the consistency of manufacture of this vaccine. After that, I'll show you the data that supports the use of the pneumococcal vaccine with the routine childhood immunizations already in place, and finally, the immunogenicity that supports the catch-up schedule that we will be recommending.

The studies of the routine infant schedule will come from five studies at eight sites across the United States for about 1,500 subjects who data go into this immunogenicity subset.

The study design for all the studies that

I'll be presenting were similar. Infants were randomized to study or control vaccines, which were administered at two, four, six and 12 to 15 months of age. Serum for immunogenicity was collected at two months, seven months, 12 and 13 months, before and after the booster dose, and for a subset of subjects also after the second dose.

Serum was assayed by ELISA assay against the individual capsule of polysaccharides. Also, a subset of individuals had opsonic assays performed. I won't show these here in the interest of time, but the ELISA assay correlated quite nicely with the opsonic assay, showing that functional antibody is produced.

These are reverse cumulative distribution curves of the immunogenicity after three doses of the pneumococcal vaccine in our Kaiser efficacy study. You can see here along the X axis increasing antibody concentrations, along the Y axis the percent of subjects that achieved those antibody concentrations. The different color lines here correspond to the seven different polysaccharide serotypes, and here is the control group, here is the immunized group. You can see that the mean response of the immunized group is far higher than the control group, and if you pick any

antibody concentration along the X axis you can see a much higher proportion of the immunized group respond as compared to the control group.

I'm going to show you a series of plots to illustrate the kinetics of the antibody response. Again, here are geometric mean concentrations, and the time of dosing before the first dose, after the second dose, after the third dose, and before and after the fourth dose.

This line here represents the control group, the blue lines represent the immunized cohort in several different studies. Note that there's a decline in the control group over the first six months, this represents a decline in maternal antibody, and after that there is virtually no increase in antibody level. Contrast that with the immunized group, where there's a good response over the primary series, a decrease, a decline over the next six to nine months, as we usually see with antibodies, and I'll show in a few minutes evidence that these children are primed for polysaccharide challenge in this period of time, and then with the fourth dose a significant boost.

There are a couple of patterns that we can see. Each of these serotypes really is an individual.

This is serotype four, and here we see an early response. By the time you've had the second dose, the antibody response has peaked, and addition of the third dose does not increase the antibody response further. Contrast that to serotype 6b on the next slide, where the early response is rather sluggish, and between the second and the third dose, when you receive the third dose you see quite a good response, although even though this response is slow compared to the previous type, you already see after the second dose a significant difference compared to the control group.

Serotype 9v represents the pattern seen with all of the other serotypes, and that's a more gradual response throughout the primary series.

These data from a study done by Doctor Daum, et. al., with a previous version of this vaccine, our 5-valentvaccine, demonstrates that these infants are primed after a primary series. What you see here are children who were randomized in the primary series to receive either the pneumococcal vaccine or a control. After the third dose, the recipients of the pneumococcal vaccine developed good geometric mean titers, ranging from two to 3.9. You see the expected decline in antibody levels before the

toddler period, and all of these children were challenged with a polysaccharide vaccine in the toddler period. This is to mimic the natural exposure to polysaccharide, and you can see that in the group that was primed with the pneumococcal vaccine there's a very vigorous response to the polysaccharide vaccine with geometric mean titers ranging between six and 29. In the control group, there is virtually no response to a polysaccharide challenge, as you would expect in these young children.

So, in summary, I've shown that all of the serotypes are immunogenic and primed for polysaccharide challenge, that kinetics vary somewhat by serotype. Antibody levels declined prior to the fourth dose, but remain above pre-immunization levels and, again, these children are primed. And finally, the fourth dose boosts the response above the level seen in the infant series.

I'm now going to present briefly some data that illustrates the consistency of performance of this vaccine over several different vaccine lots.

In our consistency lot study, 340 some odd subjects at five different study sites were randomized to receive one of three different pilot scale lots, or a control where there was no pneumococcal vaccine

given, but only the routine concomitant vaccines. No significant differences were seen among lots, as is illustrated in this next slide. Again, this is a reverse cumulative distribution curve. This is the control group, and here you see the three lots of pneumococcal conjugate vaccine, and you can see that these curves virtually super impose, there were no differences in response among these three lots.

We also did a bridging study, which compared the pilot lot to two manufacturing lots, and again, a control group, and this is the control group, and the pilot lot and the manufacturing lot again had an antibody response that was equivalent, as is illustrated by these superimposed lines in the reverse cumulative distribution curve.

Okay. I'm going to present a series of slides illustrating the response to the usual routine childhood immunizations that will be administered along with this vaccine. And, we looked at virtually all of the routine vaccines that are administered at the times that they are usually administered, as shown in this slide.

You'll see data on both geometric mean concentration and also the percentage of subjects that achieved levels that have been associated with

protection, and I've listed these here so that I don't have to list them on the subsequent slides. Note here that the pertussis antigens, we're using an arbitrary but convention of a four-fold rise because there are no levels that have been associated clearly with protection for pertussis.

Okay. What we are looking at here are children who received concomitant DTaP in the primary series. The antibody responses that you see are those achieved after three doses in children who received simultaneous pneumococcal vaccine, compared to a control group that do not receive any pneumococcal vaccine. Geometric mean concentrations first focus on diphtheria and tetanus. You can see a good response in both groups. For diphtheria, there's no statistical difference, for tetanus 3.5, 4.1 in the control group, this does reach statistical significance, but note 100 percent of children achieve a level of 0.1 international units per ML.

For the four pertussis antigens, PT, Fimbriae, 69K or protactin, in FHA there were no significant differences between recipients of the pneumococcal vaccine and the control group. We did see a difference for Fim only in the percent achieving a four-fold rise, with a lower response in the

pneumococcal group, but the other three antigens showed no significant differences.

Again, looking at DTaP, this time after the fourth dose, for diphtheria and tetanus we see a statistically significant difference for diphtheria with a slightly higher response in GMCs in the control group compared to the group that received the pneumococcal vaccine, but 100 percent of infants achieved titers of .1 micrograms per ML or greater. For tetanus, there were no statistically significant differences. Looking at the four pertussis antigens, we see differences in favor of the control group for pertussis toxin and for Fimbriae. The percent responders is somewhat closer, except in the Fim group, but none of these achieved statistical significance as differences.

The Hib response after the third dose, and I should point out that the Hib vaccine that we used here is the Hib vaccine manufactured by Wyeth which contains the same carrier protein, the CRM, and some studies with other carrier proteins have shown some interference at this level, and, in fact, we've not shown that, and have shown some augmentation of response. These are two different studies. These are the GMCs which are higher in the recipients of the

pneumococcalvaccine, as compared to the control group in both studies, and in the second study this achieved statistical significance. We see good response rates at both .15 and 1.0 micrograms per ML.

Interestingly, looking at the Hib response at the fourth dose, there is a decreased response among pneumococcal conjugate recipients compared to the control group. It is possible that this is beginning to represent some carrier limitation, but the responses are very high and a very high percent of children, 100 percent greater than .15 and almost 98 percent greater than 1 is seen, so this is unlikely to have any clinical significance.

We have one more study here, where the Hib response after dose four was looked at. This study did not have a control group, but you can see that the geometric mean titer achieved is very similar to the one achieved in the previous study, 100 percent of children achieved a titer of .15 and 88.5 percent achieved a titer of greater than or equal to one.

This is IPV, again we have pneumococcal group and children who did not receive the pneumococcalvaccine, who received IPV at two and four months of age. For polios type one, two and three, these are the percentages of children who achieved a

titer of at least one to ten, which is the lowest dilution in this assay, and that's been associated with protection. There are no differences between the two groups.

Here we are looking at hepatitis response. We looked at two different hepatitis vaccines, the SmithKline vaccine administered at zero, two and six months of age, and this should be down here actually, this is a study with a control group, and you can see that the percentage of children who achieved at least ten micro international units after immunization was very similar in these two groups, with overlap between confidence intervals. We have a second study where we looked at the Merck vaccine administered at two, four and six months of age, and almost 93 percent of children responded at the protective level, again, confidence intervals are similar to what we saw before.

For measles, mumps, rubella, we do not have a control group, but I have two different studies that were done to look at response to concomitantly administered MMR and varicella in the toddler period. For measles, we see a 94 to 96 percent seroconversion rate. For mumps, 80 to 82 percent, and for rubella, 89 to 95 percent, for varicella, 95 percent response

rate.

In summary, the pneumococcal conjugate vaccine may be given concomitantly with all of the routine childhood immunizations in this current series.

The last part of the immunogenicity part of my talk will address the catch-up schedule that is recommended for this vaccine. Children who are unvaccinated and over six months of age, if they are seven to 11 months of age we are recommending that they receive three doses, two doses separated by at least 28 days, with the third dose after the one year birthday, at least two months after the second dose. If children are 12 to 23 months of age at their first dose they should receive two doses two months apart, and children over 24 months of age should receive one dose. You can see that these recommendations are a little bit different than the haemophilus recommendations, and 1'11 show you why in subsequent slides. First, a slide that gives you an idea of the number of subjects studied and the different schedules that were studied in six different studies.

Okay. This slide will take a little bit of orientation. First notice these two red bars. These represent the antibody concentrations achieved

in the Kaiser efficacy study. In children who receivedpneumococcalvaccine together with whole cell DTaP vaccine or pneumococcal vaccine together with ace11 DTaP vaccine. Doctor Black will present you the details of the Kaiser efficacy study later, but this study was started late in '95, so the switch to acellular pertussis vaccine happened halfway through the trial and we do have two populations with concomitant vaccine.

I'm drawing here a line that will serve as a reference to titers that should be achieved by children received a catch-up schedule. This is antibody concentration along the Y axis, and what you can see are different schedules that we looked at. These are children seven to 11 months of age who received two doses and three doses, 12 to 17 months of age, one doses, two doses, 18 to 23 months of age, one dose, two doses, and over 24 months of age, one dose, 36 to 59 months of age, five to nine years of age, and what you can see is that for children who received only one dose, if they are between 12 and 23 months of age, they don't achieve levels quite as high as the reference Kaiser study and, therefore, for those age groups we are recommending two doses. This is serotype 6b, but it's fairly representative of the

other types.

Okay. In summary, Prevenar, the pneumococcal conjugate vaccine, is immunogenic in infants and primes. It shows consistent immunogenicity. It can be administered with routine childhood vaccines, and the data support a catch-up schedule.

I'm going to switch gears now and present the reactogenicity of the vaccine, specifically, the information on the incidence of local injection site reactions and also the more common systemic reactions that are commonly seen after routine childhood vaccines. After my presentation, as part of his presentation, Steve Black will talk about the remainder of the safety data on this vaccine.

From the Kaiser study, a subset of the children in the study were selected for telephone interviews for study of these common events. Children were selected by the last digit of their medical record number. Scripted interviews were held at 48 hours and 14 days after each dose, and a total of 17,000, almost 17,500 interviews at 48 hours were performed for children who got concomitant whole cell DTP vaccine and 3,500 interviews for children who got concomitant ace11 DTaP vaccine.

This graph illustrates erythema at the injection site in children who received -- okay, we are looking at injection site reactions after the first dose, second dose, third dose and fourth dose. Erythema, any erythema is represented by the height of the bar, erythema of greater or equal to an inch is represented by the yellow part of the bar. We look here at the site of the pneumococcal vaccine compared to the site of whole cell vaccine, or in other children at the site of the pneumococcal vaccine compared to the site of the acellular vaccine.

In this slide, focus on the first two bars at each dose, which compare pneumococcal vaccine to whole cell vaccine. You can see that there's substantially less reaction at the site of the pneumococcal vaccine compared to whole cell vaccine and this is significant for all four doses.

I'm going to look now separately at the DTaP site compared to the 7-valent site, because this is the routine immunization schedule at this time.

Okay. Notice first that the scale has changed here, that's why the bars are bigger. Each dose at the 7-valent pneumococcal site, compared to the acellular pertussis site, you can see that there's a slightly higher incidence of erythema at the

injection site at all four doses, but this only reaches statistical significance at the first dose. At the fourth dose, there's also a statistically significant difference. Recall, though, that with DTaP, with succeeding doses, you usually get an increased reaction rate. It's lower here at the fourth dose because these children did not receive four doses of DTaP in their schedule, a lot of these kids had some whole cell vaccine as part of their primary series.

This is induration at the injection site, and a very similar pattern is seen to what I showed you for erythema, and this is tenderness, again a similar pattern, although here nothing reaches statistical significance.

I'm going to show you results from two studies in which 7-valent vaccine plus routine vaccines were compared to routine vaccines alone, and we'll use these studies to illustrate the incidence of common systemic events within 72 hours of vaccine.

In one study, the routine vaccines administered were DTaP, OPV and Hib. In a second study, the vaccines administered were DTaP, Hib, IPV at two and four months, and Hepatitis B at two and six months.

Okay. YOU can see the reaction rates after dose one, dose two and dose three in the pneumococcal group as compared to the control group for a number of different events. Notice that for fever at the first dose the fever is somewhat lower in the pneumococcal group, although for dose two and dose three it's higher in the pneumococcal group. None of these are statistically significant. Drowsiness does reach statistical significance with a higher rate in the pneumococcal group after dose three, and we did note that there's an increased use of antipyretics in children after the second dose, indicating that, perhaps, there is slightly more reactogenicity at this dose level.

This is a different study, again, though the same setup, pneumococcal vaccine compared to children who just got the routine immunizations without the pneumococcal vaccine. Here you see a statistically significant difference in the rate of fever, greater than or equal to 38 degrees centigrade after dose one, and after dose two. If you look at fevers greater than 39, there is at dose two a slight tendency to an increase in percentage, and none of these children had fevers greater than 40.5. We see a statistically significant increase in irritability,

again, with the second dose, drowsiness here, and decreased appetite here.

What I've done here is I've combined the reactogenicity data across all the studies that we've done in infants for this vaccine, for fever, drowsiness, fussiness and decreased appetite, this is the primary series, systemic reactions were measured within two or three days, depending on the study, and I've combined all three doses of the primary series. The pink bars represent children who received the pneumococcal vaccine as the same time as the whole cell DTP vaccine. The blue bars represent children who receive it at the same time as the acellular vaccine, and the green bars are children who received routine immunizations including acellular pertussis vaccine alone, without the pneumococcal vaccine.

First, you can see that the highest responses, the highest reaction rates are with the whole cell vaccine. It's substantially lower with DTaP vaccine, but the addition of the 7-valent pneumococcal vaccine does seem to add a slight increase in reactogenicity rate.

These are similar graphs, only for the booster dose. Again, this is pneumococcal vaccine with whole cell vaccine, with ace11 vaccine, and this

is the pneumococcal vaccine alone without concurrent routine childhood vaccines. The rate in the standard schedule of pneumococcal vaccine with DTaP vaccine is a little bit higher than the pneumococcal vaccine alone, similar for drowsiness, fussiness and decreased appetite, but much less than what you see with concomitant whole cell vaccine.

I want to focus in on the fever because it's sometimes hard to see the fever breakdown in those bars, so this is dose one, dose two, dose three, dose four across all of our trials, fever rate of greater than or equal to 38 degrees with concomitant whole cell, with concomitant ace11 and with ace11 vaccine alone without the pneumococcal vaccine there is a slight increase in the rate of fever, particularly, after the second dose.

On the next slide you can see fevers of greater than 39, again notice with whole cell vaccine it ranges from 1.3 to 5.2 with an increase with subsequent doses. For DTaP vaccine, plus pneumococcal vaccine, it ranges from .8 to 2.8 and, again, there seems to be a slight predominance at the second dose, and the rates for DTaP range between zero and .6 percent.

To conclude, we see mild transient local

and systemic reactions similar to that seen with other childhood vaccines. For local reactions, the rate is significantly lower at the pneumococcal vaccine sites compared to the whole cell vaccine site, but similar or, perhaps, slightly higher than at the ace11 site. We don't see an increase with increasing dose number. For systemic reactions, there is a slightly higher rate of summary actions when administered with routine vaccines compared with when the routine vaccines are administered alone.

Okay. I want to now introduce Doctor Steve Black, who will present the data from the Kaiser efficacy trial and the remainder of the safety data for these sets of trials.

DOCTOR BLACK: Good morning, everybody.

What I'd like to do this morning is to describe to you the results of the Kaiser Permanente efficacy trial which was conducted in northern California in 37,868 children.

There are several characteristics of Kaiser Permanente which facilitate conducting this trial. Kaiser Permanente is a comprehensive integrated HMO with 2.8 million members in northern California. There is a birth cohort of about 30,000 children per year, and there are automated centralized

bacteriology laboratories services with associated databases, as well as databases for clinical information services. A unique medical record number is assigned to members at birth and allows us to track events across laboratory and utilization databases.

Kaiser Permanente is also self-insured, and what means is that members seek care, either emergency or referral care, outside the system, that is submitted back for reimbursement and allows us to identify those events as well. In addition, there's an extensive research infrastructure which facilitated this trial.

We did some preliminary studies prior to the trial, which looked at the incidence of disease in our population, and I'd like to show you those results now. What you see here is the incidence of invasive pneumococcaldisease within Kaiser Permanente in cases per hundred person years, in years prior to the trial, 1988 to 1991, compared to data from the U.S., from the active bacterial core surveillance system from CDC in 1998. And I think what is striking here is that the incidence of disease is very similar between our site and the national data, with a slightly higher incidence in the youngest children in the CDC data.

We also in a separate study looked at the

sera epidemiology of disease, and we determined that approximately 83 percent of invasive disease was accounted for by the seven serotypes in the heptavalent vaccine.

So, I'd now like to describe the study to you and the study results. There are several study components, safety surveillance, Doctor Hackell described to you the results of the telephone interviews that were conducted. We also had surveillance for rare events, using automated data sources for all emergency and hospital visits, as well as looked at clinic diagnoses. We did serology on two subsets of children, which Doctor Hackell has reported on, and there are several efficacy outcomes which I'll describe to you in a moment.

The study design was a randomized, double blind control trial with one-to-one randomization. Children were either assigned to receive the 7-valent pneumococcal conjugate or a meningococcal c conjugate vaccine. This vaccine was chosen as the control for several reasons, one of them is that it's visually identical to the pneumococcal conjugate vaccine. We also felt that offering the potential of some benefit to these many children getting four doses of vaccine would facilitate enrollment into the trial.

Healthy infants were targeted for enrollment at two months of age, and the immunization schedule was two, four and six months, with a booster between 12 and 15 months of age.

Invasive disease was the primary endpoint in the trial, and specifically the primary endpoint was invasive disease due to vaccine serotype in children vaccinated per protocol. Cases had to occur at least 14 days after the third dose of vaccine, and they had to occur in immunocompetent subjects. Secondary endpoints included invasive disease analyzed in an attempt to treat format, in which follow-up began as of the randomization of the children at the time they signed consent. And, in addition, invasive disease due to any pneumococcal serotype was evaluated, both in per protocol and intent to treat format.

This was a group sequential design with one interim look analysis that was planned at 17 cases of invasive disease due to vaccine serotype. The plan total sample size was 26 cases, and the stopping rule was that at the look at 17 cases we would stop the trial if there were two or fewer vaccine failures.

The study utilized a study advisory group, which was independent of the investigators of the

sponsor. They had several functions, one of which was to monitor the safety of the study as the trial progressed. They had the option of unblinding if there were safety concerns, but that was not done, there was no unblinding that took place prior to the interim analysis, and the members of the study advisory group are shown here.

As of the time of the identification of the 17 cases of per protocol invasive disease due to vaccine serotype, the following procedure took place. A list of all the cases of disease, in vaccinated and partially vaccinated children, was sent to the study advisory group members, and the blinding key was sent to the advisory group members under separate cover by the project statistician.

During a conference call, the study advisory group unblinded cases, and because the interim stopping rule was met we, as the investigators, were notified of the case split in the trial.

So, let me describe the study population to you. Northern California is a very diverse area, racially and ethnically, and our population represents that or reflects that. What you see here is the racial ethnic composition in the pneumococcal group,

the meningococcal group, and the entire Kaiser Permanente birth cohort during that time period, and what you can see here are several things, is that the randomization was quite successful and that the distribution here between the two groups is very similar. But then also, we recruited a population which was very representative of our population as a whole.

As of the time of the interim look, there was 37,868 children in the study, as I mentioned to you, and these are the number of children who had received at least one dose, two dose, three dose, or four doses during the trial. You can see again, these numbers are very similar between the two groups.

The age of vaccination is shown here, the mean age of vaccination, and this was virtually identical in the two groups as well.

There are several follow-up dates that I'll be talking about in these results, and I want to show you these in advance, because they can be confusing. The primary safety analyses was through April 30, 1998, and we looked at safety there, otitis media, tube placement and pneumonia. The interim analysis, as I described to you, was on August 20th of 1998, and there's also results of a reporting on

extended efficacy, safety analyses and spontaneously draining ears as an outcome through April 20th of 1999.

This slide shows the cumulative follow-up in the two different analyses, as of the first of each of these months, and what you can see here is that in the per protocol analysis the numbers are very similar between the two groups, and similarly, in the intent to treat analysis that's true as the study progressed.

So, we were quite happy to hear from the study advisory group the following results, and I think many of you have heard these already so I'll go through them rather quickly. But, in the per protocol analysis, all 17 cases of invasive disease due to vaccine serotype were in the control group, for a point estimate for efficacy of 100 percent and the lower bounds 75.7 percent. In the intent to treat analysis, which includes both fully and partially vaccinated children, all children in the study, again, all cases were in the control group, point estimate for efficacy is 100 percent and the lower bound is 81.7 percent. For someone with my level of statistical sophistication, I was glad that it was this black and white.

These are the diagnoses that we observed

as of the time of the interim look, and what you can see here is, of the 22 cases the majority of them were bacteremia, but there were two cases of meningitis, three of sepsis, one of cellulitis and one of pneumonia.

This looks at serotype specific effect. Well, actually, this is just the number of cases, all in the control group, by serotype here, and you can see the case splits as they occurred.

This looks at effectiveness of the vaccine against the total disease burden, due to pneumococci, in other words, what we are doing here is looking at all of pneumococcal invasive disease cases regardless of vaccine serotype. In the per protocol analysis, there are two cases in the pneumococcal group, 20 in the mening., for an impact of 90 percent of total disease burden. In the intent to treat analysis, there is a 88.9 percent reduction in total disease burden.

I'd now like to report to you on the extended follow beyond the interim look, up through April 20th of this year. Enrollment was terminated, as I described to you, in August of 1998, but blinded immunization continued per protocol until April 20th, at which time we received permission to offer the

pneumococcal conjugate vaccine to the control group and the study was unblinded. During that interval, blinded immunization per protocol continued, and the study nurses, physicians and parents remained blinded, as was the case ascertainment as well.

These are the results as of April 20th of 1999. In the per protocol analysis, there were 39 cases, in the control group, and one case in the pneumococcal group, and a fully vaccinated child after four doses of disease, and that child was apparently healthy as far as we know. In the intent to treat analysis there were three children in the pneumococcal group who developed invasive disease. The one case I just described to you in the per protocol analysis, one child had received only one dose of vaccine and then developed invasive disease almost a year later, and the third child, though, had acute myelogenous leukemia and was immunosuppressed due to chemotherapy. The overall impact here is 93.9 percent in the intent to treat analysis.

These are the diagnoses as of the time of that look, and what we can see here is that there are two deaths in the population, one child died of meningitis in the control group, one child died of bacteremic pneumonia in the control group as well.

If we look at bacteremic pneumonia as a specific outcome, and these are children who had pneumonia, but also had invasive disease at the same time as evidenced by positive blood culture, in a per protocol analysis what we see here is seven children in the meningococcal group, one in the pneumococcal group, a point estimate for efficacy of 85.7 percent, which is not statistically significant. However, in the intent to treat analysis, the case split is 8/1, the efficacy is 87.5, and that is statistically significant. And, interestingly enough, if you look at all serotypes we see a 90 percent reduction of disease which is statistically significant as well.

This looks at serotype specific efficacy, and in an intent to treat format. Again, where fully and partially vaccinated children are included, and we can see that we have sufficient power to demonstrate serotype specific efficacy in five of the seven serotypes, and not sufficient power to do so for 6b or 9v. You'll not that there are only six serotypes listed here, type four there were no cases during the entire study period in our population.

If we look at this by dose number, we can see interestingly that children who received one or two doses of vaccine, although it's not statistically

significant, there is a 7/1 case split suggesting efficacy of partial vaccination in a schedule of three primary doses and then a follow-up booster dose.

If we look at non-vaccine serotypes here, we also see a suggestion of an effect as well. The serotypes shown in yellow are potentially cross reacting serotypes, of which you can see there are three out of six total cases in the meningococcal group, control group, are potentially cross reacting. There are only three cases in the pneumococcal group, one of which is potentially cross reacting, and actually this child had a thyroglossal duct cyst abscess, this is not a bloodstream infection. The drainage of that abscess is what yielded this organism.

If we look at all serotypes as of April 20th, we see a 92.9 percent reduction in total disease burden per protocol, and virtually almost 90 percent, 89 percent reduction in total disease burden in the intent to treat analysis. So, we've interpreted this to mean that at least during the course of there's trial there's no evidence of replacement, and there might be some evidence of cross protection, given that initially we estimated 83 percent coverage by the seven serotypes.

I'd like to reshow you the incidence slide I showed you earlier. This is the U.S. incidence from the active bacterial core surveillance from CDC. This is the pre-study results which I showed you earlier as well, and this next column is the incidence of invasive disease in the control group, and there's a remarkable similaritybetweenthe incidence of disease in the control group in the study to the pre-study results that we identified earlier.

I'd now like to talk to you about otitis media. Otitis media, there are several outcomes. Visits for otitis media were routinely captured from electrically scanned or optically scanned forms. An episode for the purposes of analysis was defined when a visit was not considered a follow-up visit, and I apologize for the double negatives here, but it's actually easier to explain this way than the other way. A visit was called a follow-up visit if it occurred within three weeks of another visit for otitis media, or if it occurred four to six weeks from a prior visit and a visit — appointment for that second visit was scheduled more than three days in advance, indicating this was not due to an acute illness. So that, if we took all the visits and then subtracted the follow-up visits out, we came up with

episodes. We also looked at frequent otitis using several definitions, and I'll show you what those are, tube placement and serotype specific efficacy.

This is intended as a frame of reference, and we could spend the rest of the afternoon arguing as to what the real numbers are that go in these boxes, but I just want to let you know that the clinical episodes of otitis media we're talking about are any visit where a physician made the diagnosis of otitis media. These individuals were not cross trained, there were more than 500 observers, and this is more the reality of what gets called otitis media in the clinic. Of those, we estimate from literature and talking with Doctor Jerome Klein, that 50 to 60 percent of these are likely to be bacterial, and between 20 and 40 percent, depending on whether you use U.S. or Finnish data, would be pneumococcal, and then 60 to 85 percent of those might be vaccine serotype.

The important point here is not these total numbers, but the fact that overall we have to anticipate we are not going to see 100 percent effect against otitis media, the total potential impact is likely to be between six and 20 percent.

These are the number of events that we had

available to analyze. There are a lot of them. There were more than 47,000 visits in the per protocol analysis, 73,000 visits in the intent to treat analysis.

These are the results in the per protocol analysis, and what we see here is there was an 8.9 percent reduction in the number of otitis media visits in the pneumococcal group, a seven percent reduction in the number of episodes. However, if we look at frequent otitis media, the more frequent we make the definition we see an escalating effect of vaccination, such that if we start with three visits, three episodes within six months, or four or more within a year, we see a 9.5 percent effect on up to five or more episodes within six months, six or more with a year, we see a 22.8 percent reduction in number of children with this problem.

Similarly, for ear tube placement, there was 20.3 percent fewer children had ear tubes placed in the pneumococcal group.

These are similar results by intent to treat analysis, and rather than walking you through them let me say that they are very similar in magnitude, but smaller in each group.

We also asked physicians to, if they saw

children with spontaneously ruptured tympanic membranes, to send cultures on that drainage to the laboratory for identification of pneumococcus, and if that was identified we sent that off for typing. And, we had a total of 23 such cultures submitted during the study. YOU can see here in the fully vaccinated children, the serotype specific efficacy estimate here for this outcome was 66.7 percent, not statistically significant, and in the intent to treat analysis we saw 64.7 percent, and that was statistically significant.

So, now let me talk about safety. You've heard quite a bit about reactogenicity from Doctor Hackell this morning, and what I'd like to talk to you now is review of medical utilization to evaluate any rare events or rare adverse events that might be associated with this vaccine.

There were a lot of comparisons made here, and I think it's important to emphasize that, because the statistics that I'll be showing you have nominal p values that do not take into account the number of comparisons that we'll be reporting on. For hospitalizations, you can see there are several intervals here ranging from three to 60 days. The 60-day interval is the analysis that was specified in the

protocol, and the numbers that are shown in yellow here are the ones that were originally specified in the protocol, the ones in white are additional analyses that we've conducted.

For emergency room, we did three, 14 and 30 days, and for clinic visits we looked at specified outcomes, seizures within three days and 30 days, asthma and allergic reactions within three days.

There are also multiple comparison groups. By series, we looked overall combining primary and booster dose, and we looked at those two separately, and we also broke this down by concomitant whole cell pertussis vaccine, either one, whole cell alone, ace11 alone or neither.

Now, you don't need to read all this, but what this shows is a list of the 92 diagnoses that we identified, different diagnostic categories that we identified in children during this trial. It's important to emphasize that we did not a priori specify which diagnoses we were going to evaluate. We had evaluated all the diagnoses that occurred in these children, of which there are 92 shown here.

In addition, in the emergency room as well, there are 80 different diagnostic categories in which children have these during the trial period, and

comparisons were made for all of these. And, we've calculated for the hospital comparisons alone, and not added them up for the emergency room yet, that for hospitalizations alone, because of the 92 categories and all the other possible comparisons, there were about 1,400, a little bit more than 1,400 different statistical comparisons that were made.

Let me first go through the emergency room results, and what we see here, these are diagnoses that have statistically elevated emergency room visit rates in the pneumococcal group, again using a nominal p value which did not take into account all of the comparisons that were made. And, what this shows, let me orient you to this table, this is the diagnosis, ear poisoning and ingestion, under that it was only significantly elevated when we looked at all doses combined, not for either the primary series or the booster series alone, and this is the windows where we saw statistical significance, three days and 14 days, interestingly not the 30 day window which was originally specified in the protocol, and it was only statistically significant when we combined both DTB groups.

And, what we see here is an elevation for poisoning and ingestion in the children, given the

lack of a physiologic basis for this, we feel this is just due to the number we would expect by chance alone, because of the large number of comparisons. You see some diagnoses here.

We also saw, within the three day window only, an elevation for croup, trauma, breath holding and urinary tract infection.

This is a different type of slide, and I need to orient you to this as well. What this shows is for the outcomes which we felt were physiologically feasible. What we did is then plot the events over the time window to see whether there was any consistent time association with vaccination, because we felt that if this were a physiologic event we would see some consistent time association there.

And, what we see here is that for the five events, all in the pneumococcal group, they are spread out pretty evenly over the 30 day window. Of these events, three of them were with whole cell vaccine, two of them were in children who had no concomitant DTB, and there were no visits with concomitant acellular pertussis.

This looks at croup, which was another diagnosis from the same table, and as you can see here the events are spread out quite uniformly over the 30

day window, there does not appear to be any consistent time association.

Now we'll look at hospitalization rates, elevated hospitalization rates were seen in three categories, acute gastroenteritis for both all doses and the primary series alone. In fact, we can see here that it's the primary series that's driving this, really, these are shown as two separate lines, but this group, the primary series, is a subset of the all doses group. We also saw for febrile seizures, for all doses and in the primary series, just in the 30 and 60 day window, 'interestingly enough, not in the shorter time windows. And, asthma, only over the 60 day window, and only for the DTaP group.

I should emphasize that for the seizures this was only seen in the whole cell group.

This looks at hospitalizations for gastroenteritis. I'm glad we didn't have a longer time window, because it wouldn't fit on the slide, but we see here is that the events for gastroenteritis are, again, spread out over the 60 day window, with no consistent time association.

That was with all vaccines, what this looks at is with whole cell vaccine alone. Again, we see that this is spread out over the whole window, and the

next slide, if we look for DTaP alone there really are very few events altogether.

We looked also at seizures, and one of the things that we looked at is seizures within three days, because we felt that that's when fever is seen with vaccination, as you saw, and if there was going to be an increased risk this was where we would see that. These are identified from any source, and I'll explain to you what that means in the following slide in a moment, but you can see here that there were seven events with whole cell in the pneumococcal group, three in the meningococcal group, that's not statistically significant, but I think even more important there's only one event each in each group in the DTaP children.

And, what this slide shows is that the subset of the children in the prior slide, who had seizures within three days, who had seizures with fever, and what we see here, of the children who had seizures with fever in the pneumococcal group, and this is hierarchical, so if they were seen in the hospital we didn't list them again in the ER, and so on down the line, there were no children hospitalized within three days. Three were seen in the emergency room in the whole cell group. Two of them had urinary

tract infections, as the source for their fever, and in the DTaP group the one child who had a febrile seizure had a viral syndrome that was most compatible with roseola. So, again, another cause of the seizures within this short three day time window, and if you were willing to attribute that seizure to the viral illness there were no febrile seizures in either group in association with DTaP vaccine.

Because we were looking at fever, and because fever was seen as being increased following dose two, for example, in the data that was presented by Doctor Hackell, we also looked at emergency room visits for any febrile illness in the 30 day window, and what you can see again is that it's relatively uniform over the 30 day window, but there does seem to be a suggestion, which is not statistically significant, and, perhaps, a little more visits to the emergency room early on in the window.

If we break this down by whole cell vaccine, we can see that this pattern persists, although you can see there are other bars further out during the window. For DTaP you can see that that pattern disappears, that there really does not seem to be any suggestion of that.

Asthma was another event that showed up as

increased on the hospitalization table, and, again, we see in blue for the pneumococcus there is no suggestion of any consistent time association with vaccination. We see this with whole cell pertussis again, and acellular pertussis as well.

I'd also like to talk to you about the clinic events. The clinic diagnoses that were evaluated were allergic reactions, neurologic reactions, asthma and wheezing, and there was no significant elevation for any of those in the pneumococcal group within the time windows that I showed you earlier.

Now, one of the things that we were asked to do by statisticians at the FDA was to look at selected hospital diagnosis any time during the study, and it's important you understand this is a different analytic framework than what I showed you. This is basically designed to look for chronic illnesses, because we are taking children once they are enrolled, and if they develop this diagnosis any time from the beginning of the study to the end of surveillance we included those hospitalizations in this table.

And, the diagnostic categories that we were asked to evaluate were aplastic anemia, autoimmune disease, autoimmune hemolytic anemia, diabetes,

neutropenia and thrombocytopenia. And, I'll show you first the results of the automated data and then results of chart reviews which followed. You can see here that the case split is four in the meningococcal group, six in the pneumococcal group, and there's an extra column here. And, what we did, our site is part of the vaccine safety data link project funded by the CDC, and we took the data set from 1995 from CDC, which was largely prior to this study, from our site and calculated in the age group of the study population how many cases we would expect to see in each group. So, here we have four in the mening. group, six in the pneumococcal group, we would expect six in each group. This is very consistent with that.

For autoimmune disease, there's 17 in the meningococcal group, 11 in the pneumococcal group. We'd expect 16 in both groups, et cetera.

For diabetes, there are five in the meningococcal group, one in pneumococcal group, we would actually expect 11 in each group.

So, let me go through each one of these when we reviewed the charts and tell you what we found. For the children who has aplastic anemia coded as one of their diagnoses in a hospitalization, one of the children had chronic anemia secondary to pertussis

infection, another child had anemia and salmonella gastroenteritis, another child anemia secondary to chronic renal infection. So, three of them were due to -three of the categories were due to infection and associated anemia, and the largest category by far was anemia and neutropenia, secondary to cancer or cancer chemotherapy.

In terms of autoimmune disease, this is what we found. The largest diagnostic category here was Kawasaki's disease, and the other categories are shown. There's one child in the meningococcal group with ITP.

For autoimmune hemolytic anemia, we have one child here who will show up again in another diagnostic category for another hospitalization, who has a congenital defect in terms of bone marrow function which leads to anemia and neutropenia, who is in this category in the pneumococcal group.

For diabetes, as I showed you, the case split is 5/1. There's another child who expired due to diabetic keto acidosis, who was not included in these results because the child was not hospitalized, died in the emergency room, so this is our experience with diabetes in the study overall.

For neutropenia, what we see is the majority

of these are secondary to cancer and cancer chemotherapy. There was one child with neutropenia in the meningococcal group, and there's another child reported by a nurse with chronic neutropenia who was not hospitalized within Kaiser Permanente that we are aware of. That's the total experience in our population.

For thrombocytopenia, these break down into children with cancer, and ITP per se you can see that there are three in the meningococcal group, three in the pneumococcal group, an even split. There are other cases of thrombocytopenia in the study population, one hospitalization outside of our program due to ITP and two nurse reports, both of those are in the meningococcal group.

We also looked at deaths in the study population overall. These are the categories, the diagnostic categories associatedwithmortalityduring the study. You can see the ns here and the interval in days since most recent vaccine here in the pneumococcal group and in the meningococcal group. The only diagnostic category with a substantial number of cases is SIDS, and I'll show you a separate analysis for that in a second.

We looked at SIDS in two ways. What we did

is, using the 1995 to 1997 California Mortality Tape, which allowed us to calculate an age and season adjusted expected number of events in the study population during the study period, and that's shown here, expected number within one week for the pneumococcal group is 1.06, we observed one, the expected within two weeks is, essentially, two, we observed two, and you can see up to a year of age in children overall we would expect eight cases in the pneumococcal group, we observed four, in the meningococcal group we expect eight, we observed eight.

Another way of looking at this, SIDS rates are also commonly presented as rates per thousand children during the first year of life, for the pneumococcal vaccine that rate was .2, .4 for the meningococcal group, and from 1996 and 1997 data from California, again, at age matched to our population, and eliminating cases less than two months of age, because that's the age at which children are enrolled into the study, the expected rate from California would be .5, both of these rates are lower than that.

We also looked at HHE in the study population. This was ascertained through the 48 hour telephone interviews, and if the parents stated that

the child was weak, limp or floppy, the child was considered a potential case, and these were evaluated by further interview through the study nurse and then reviewed by one of the two principal investigators, myself or Henry Shinefield. Through this surveillance, we identified one case of HHE, with a classic presentation two to three hours of duration out of 8,752 interviews in the pneumococcal group. There were no cases in the DTaP group or in the mening. recipients.

Doctor Hackell asked me to summarize these events from other trials outside our own, and these are events that were considered at least possibly vaccine related in other trials. The most common of these was fever, and what you can see here, there are only a couple HHE events that were associated with whole cell pertussis vaccine again, and only one SIDS case 47 days after receipt of vaccine.

so overall, we conclude that the pneumococcal conjugate vaccine was highly effective in preventing invasive disease, due to the seven vaccine strains used in the vaccine, when given in a two, four, six month schedule, with a booster dose in the second year of life. There was a significant reduction of otitis media, and that was most prominent

for children with frequent otitis media or tube placement, and that the pneumococcal conjugate vaccine was associated with mild and self-limited local and systemic reactions, and not associated with serious adverse events.

Thank you.

CHAIR GREENBERG: Thank you, Doctor Black, that was maybe the largest download of data in the shortest period of time that I've been associated with.

George, how much more —

DOCTOR SIBER: Mr. Chairman, I will be extremely crisp. I'll try to be.

In conclusion, just to summarize, the safety profile you've seen is comparable to other childhood vaccines for Prevenar. There's a high level of efficacy against serious disease. We saw significant reductions in clinical otitis media. We showed you that it was compatible with other childhood vaccines, and the epidemiologic data suggests that it will be directed against most of the antibiotic resistant pneumococci.

The point I want to make really is that I think Prevenar, if introduced, has the potential to substantially reduce the disease burden of the single,

most common invasive bacterial pathogen of children. From a public health vantage, Prevenar has the potential to reduce the use of antibiotics and, thus, to reduce the pressure on bacteria to become resistant to antibiotics.

We have calculated approximately how many cases of pneumococcal disease would be prevented by the general introduction of Prevenar, and with a single birth cohort of one year, and we've used for this the CDC disease rates, age specific disease rates, the percent coverage, vaccine serotypes that you've heard about, and the efficacy estimates from the Kaiser study that you just heard.

So, in a single birth cohort, assuming efficacy up to 16 months of age, but not beyond, one would expect to prevent more than 13,000 cases of invasive disease, more than 1,000 cases of meningitis, 1.3 million otitis media visits, and more than 60,000 cases of PE tube surgical procedures.

Made more graphic, perhaps, is if all U.S. children were immunized with Prevenar we would prevent three cases of meningitis, 37 cases of invasive disease, 173 PE tube procedures and 3,800 otitis media visits every day.

I really want to thank, at this point, the

many investigators. Shown here are only the subset of investigators who worked on the studies contributing to this PLA, these have been terrific collaborators for us and are responsible, I think, for the quality of the data that you are seeing today. I'd also like to thank colleagues at NIH, and I see Doctor Bill Jordan in the front row, under whose auspices I think the pneumococcal work was initiated and is coming, I think, to fruition.

I'd also like to thank our colleagues at FDA, who have done an enormous amount of work, especially in the last six to nine months, reviewing these data in a very timely manner.

Thank you.

CHAIR GREENBERG: Thank you, and I'd like to thank the manufacturer for really adhering to time lines. We have — I hope all of you got all of that, and we're ready to ask some questions.

Doctor Kim?

DOCTOR KIM: Let me begin by asking some specific questions related to immunogenicity. I know you talked about ELISA and opsonic antibody, and then I presume that in the future pneumococcal conjugate vaccine of this nature will not, perhaps, go through the clinical trials as we heard today. So, based on

the data available, what would you say that a protective level of antibodies for each serotype or, you know, different serotypes, and/or would you say that level of antibody would be comfortably extrapolated to other vaccines of this nature?

DOCTOR SIBER: What a set up.

I could spend quite a long time talking about protective levels of antibody to pneumococcus. In the interest of time, I think it's fair to say that looking at the reverse hemolytic distribution curve, and if one picks a population based method for discriminating between the protective immunized population and the unimmunized at-risk population, you can see that levels in the order of .15 to .5 can be chosen as protection.

There's been intense debate between FDA and ourselves about precisely where that might be, and I think we probably have not reached a firm conclusion, but I think it will be possible to define protective levels, which is really what you are asking about, which will facilitate, I think, in the future the development of combination vaccines or other pneumococcal conjugate vaccines and so forth.

DOCTOR KIM: And then second question related to that is, since this vaccine is introduced, then it

will be given to very young infants. Is there any information available regarding the effect of anybody under immunogenicity of these vaccines?

DOCTOR SIBER: That's a good question, actually. It's one that I have raised a couple times. I'm not sure that we have done a formal analysis of that. Jill, are you aware of a formal analysis -yes, Bob Kohberger is going to address that question.

DOCTOR KOHBERGER: In most of the analyses of the immunogenicity, if we put the pre-value and use it as an adjustment to what we get for the post, in general we don't find that it's correlated, so that the pre-level doesn't seem to interfere or change the response.

CHAIR GREENBERG: Doctor Daum and then Doctor Snider.

DOCTOR KIM: Can I ask one more to Doctor Black?

CHAIR GREENBERG: Yes.

DOCTOR KIM: If I understand, I guess after April or May, 1999, that all individuals have been offered this conjugate vaccine. Is there any data or information available that, indeed, invasive pneumococcal disease in your organization has decreased by 80 to 90 percent, let's say, from April,

May up to now, about six months of time, for any analysis you have done?

DOCTOR BLACK: That's an interesting question, and I think you are trying to get at, perhaps, herd immunity or other things. And, you know, if you look within short time windows, which six months for pneumococcal epidemiology is relatively short, there's so much variation anyway, it's difficult to say.

I can tell you that since April 20th we've only had two cases of invasive disease, but we've had similar time windows in the past where that's occurred. So, I think we need to wait longer.

CHAIR GREENBERG: Doctor Daum, then Doctor Snider.

DOCTOR DAUM: I also join in congratulating you all for a really amazing presentation this morning. I found it very helpful.

I'm sort of excited about the idea of being able to remove some of the antibiotic pressure on these organisms, and thereby diminish rates of antibiotic resistant pneumococci, but a concern, potentially at least, is that we are going to put, as we phase in this program of immunizing every American child, every child in the world hopefully, a different

kind of pressure on the organisms, as an antibody pressure. And, this organism, unlike many others, is less offended by taking up for a DNA, or DNA from another organism, and thereby being able to change its capsular serotype without modifying a whole lot else in its genetic make-up.

And so, I guess I'm wondering, on a philosophical, thoughtful basis, what kind of program do you believe should be put into place, if any, to look at serotypes causing invasive disease, colonizing children, or causing otitis media for that matter, after we introduce this program on a mass scale.

DOCTOR SIBER: Well, it's actually not mine to comment on, the program that should be put in place, but what I can comment on are what we as manufacturers are thinking about. To begin with, with colonization studies that have been done in South Africa, as well as by Dagon Ron in Israel, it's been clear that about 40 to 50 percent reduction occurs in carriage of vaccine type pneumococci. There's also a reduction in carriage of a cross reactive type 6a.

At the same time as that occurs, there is an increased rate of carriage of non-vaccine types, so that the net pneumococcal carriage is reduced only slightly, and not significantly. The question is

whether that will also result in an increased rate of otitis by non-vaccine types over time, or an increased rate in invasive disease by non-vaccine types over time, and that's a question we share your concern about. I think as you said, the pneumococcus is not offended if you take up foreign DNA and, in fact, some people have said that the pneumococcus is promiscuous in taking up foreign DAN from other pneumococci. And so, you might anticipate capsular switching over time in response to antibody pressure.

The real question is, are the types that we have been seeing now and are including in the vaccine the bad actors, and the other types have chassis', if you will, other than capsule, that are not as good as pathogenic. Well, capsules are not pathogenic, as is true for haemophilus. We don't know the answer to that question right now, but certainly would like to be ready for the possibility of this, and I think the ways that one can be ready is to increase coverage to other common types around the world that are known to have invasive potential, and I think you are aware that there is a plan to add additional serotypes to this vaccine in second and third generation products. And, the other, I think, possibility is to consider protein antigens of the organism in the tentative

capsule. There, I think, you are in a higher risk proposition because no one has really convincingly showed that these protein antigens would be effective as human vaccines, that needs to be demonstrated, but that would then take the pressure off the capsule from an immunologic selection point of view.

CHAIR GREENBERG: Doctor Snider, then Ms. Fisher, and then Doctor Stephens, and then that will be it. And, please try, panel, to formulate your questions so that they are also crisp.

DOCTOR SNIDER: George, could you remind us how much follow-up we've been looking at in terms of the efficacy data thus far, and how much is planned?

DOCTOR SIBER: I'd like to turn that question over to Steve Black, in terms of duration of follow-up in the efficacy trial.

DOCTOR BLACK: These children are just now turning four years of age, and we anticipate following this population indefinitely, so we are still following the original cohort of Hib TITER children that we immunized as well.

Does that answer your question?

DOCTOR SNIDER: So, most of -we've had about a three year follow-up, I forget what the accrual period was, I think 1998?

DOCTOR BLACK: There are several end dates, it was October of 1995 for the primary safety analysis was through April of 1998. The interim analysis was August Of '98, and then the extended follow-up was through April of this year.

DOCTOR SNIDER: So, the mean follow-up, what would you guess?

DOCTOR BLACK: About two years.

DOCTOR SNIDER: I was just thinking about the incidence that George was showing us, what we might be able to accrue with the additional follow-up period.

Thanks.

CHAIR GREENBERG: Ms. Fisher.

MS. FISHER: This is a question for both Kaiser and Wyeth-Lederle. It's my understanding that this Kaiser trial took place between October, 1995 and August of 1998, that there were 17,457 interviews of children who got whole cell pertussis vaccine in this trial, and 3,541 interviews of those who received DTaP.

In July, 1996, the FDA licensed the DTaP vaccine for the fourth — primary doses and the fourth dose, and I'd like to know why ethically Kaiser and Wyeth-Lederle used the whole cellpertussis vaccine in these trials, and it confounds the picture,

particularly with regard when the children receive whole cell pertussis vaccine and the pneumococcal vaccine, and seizures occurred, and fever, and all these other things, we don't really know whether the pneumococcal vaccine causes those reactions, because whole cell vaccine was used. And, I'd like to know why it was.

DOCTOR SIBER: I'd be delighted actually to pass that question to Mr. Black to address.

DOCTOR BLACK: Yes, at the beginning of the trial in October of '95, a cellular pertussis vaccine was not licensed for the primary infant series. And, as the recommendation for its use came about, we encouraged physicians to switch from the whole cell vaccination to a cellular vaccination. And, in fact, as of this point of time, there were a couple of transitions during the trial, one of them was for acellular pertussis, the other was from OPV to IPV as well. And, you know, the recommendations, our physicians follow the recommendations for use of vaccines, as outlined by the ACIP, and that's what was used during this trial, were vaccines that were licensed and recommended for use at that time.

MS. FISHER: It does confound the picture in terms of safety.

DOCTOR BLACK: But, that — the acellular pertussis vaccine was not available to us as part of the protocol at the inception of the trial, and that's why we conducted a second set of telephone interviews and have stratified the data by vaccine, by acellular pertussis group, and all the safety tables that I presented to you.

MS. FISHER: But, the majority of the trial was conducted after the licensure of the DTaP vaccine, there were only eight months where the DTaP was not used in infants, so I don't know, you know, Kaiser or somebody needs to get the word to the physicians that they need to use DTaP, because I think it's shocking that this many whole cell vaccines were given, vaccinations were given.

DOCTOR BLACK: Yes, just one quick comment, in that I think nationally in pediatric offices coast to coast when new vaccine recommendations come about there is a transition from one to the other, and especially when that transition involves from a combination vaccine which was very well accepted by pediatricians to two separate injections, it takes a while to change. That was true for IPV as well.

CHAIR GREENBERG: I'd like to move on now to Doctor Stephens, last question.

DOCTOR STEPHENS: I do want to commend you for an excellent presentation. My question concerns persistence of antibody levels. Your graph suggests that 60 months is, in terms of the last couple of slides you presented, impact. Do you have data that suggests that there is persistence of antibody to 60 months? That's my first question.

The second question concerns the case or cases, there's one case I know of a vaccine failure, and whether that case has been looked at immunologically.

DOCTOR SIBER: With regard to the first question, I don't believe we have data to 60 months, am I wrong about that? It's two years. But, I think I'd like to make a point on that, and that is you'll notice, of course, that antibody levels declined to 15 months, often to fairly low levels in individual patients, and we seem to have a benefit out to 15 months without breakthrough in this limited efficacy trial.

And, in fact, we seem to see a benefit even after one or two doses, although not statistically significantly so at this time. What this suggests is that priming in the case of pneumococcus may be quite important, and I think it's very clear that the

vaccine primes.

I think with pneumococcus, and I'm speculating, there's probably a period of time when you get colonized when you have a chance to mount an antibody response if you've been primed, and so I think having been primed by conjugate, even if your level drops, may give you a substantial amount of protection.

We do not have, in any group yet, six year antibody data, if I'm correct on that, two years — is it four years — two years.

With regard to your question about the single older breakthrough in immunologic status, Steve?

DOCTOR BLACK: Yes, the only thing I can tell you about that child is that the child had grown healthy, was growing well, did not have any other infectious problems, however, the parents refused to have blood drawn for immunologic analysis, so we don't have that data.

CHAIR GREENBERG: I'd like to thank the panel and the committee. We are going to take now a 12 minute break, and be back here at 11:05 to start again.

Thank you.

(Whereupon, at 10:51 a.m., a recess until 11:06 a.m.1

CHAIR GREENBERG: If people would take their seats. If people could please take their seats. Doctor Siber, take your seat.

I apologize to all of you for pushing you on the time of breaks. I hope you all were at least able to take whatever necessary things you had to do in that time, but we have a very full day and I want to move things along.

We are now going to have a CBER presentation by Doctor Douglas Pratt, and after that we'll have the ability of the committee to ask some more questions, and I know there were a few questions here that I had to cut short, and maybe we'll be able to get those. So, there may be a few questions for the manufacturer lingering from the last session as well.

Doctor Pratt?

DOCTOR PRATT: Good morning. My name is Douglas Pratt. I'm a Medical officer in the Division of Vaccine Applications, within the Office of Vaccine Research and Review at FDA.

FDA received a product license application from Wyeth-Lederle Vaccines in Pediatrics for Prevenar on June 1, 1999. The application was granted priority

review status based on the severity of the disease for which the vaccine would be indicated, that is, invasive pneumococcal disease, meningitis and bacteremia, and preliminary results indicating substantial evidence of efficacy.

Preliminary efficacy data were presented at this committee at the November, 1998 committee meeting.

Regulatory approval has been requested to market Prevenar for active immunization of infants and children, beginning as early as six weeks of age, to help protect against invasive diseases caused by Streptococcus pneumoniae due to capsular serotypes included in the vaccine.

Prevenar has also been studied for prevention of otitis media and pneumonia. The Advisory Committee will not be consulted at this session regarding those other potential indications.

study of the 7-valent pneumococcal conjugate vaccine as an investigational new drug began in November of 1994. The pivotal efficacy trial was initiated about a year later in October of '95. The safety database and databases for secondary endpoints of otitis media and pneumonia were locked on April 30, 1998, in anticipation of eminent accrual of sufficient

cases of invasive disease for a planned interim analysis. That analysis occurred on August 20, 1998, after which enrollment ceased as results indicated evidence of efficacy. That analysis is considered a primary efficacy analysis.

The otitis media analysis planned for the efficacy study was finalized later that year, and a pneumonia analysis plan was finalized in March of this year. On April 20, 1999, a follow-up of subjects for invasive disease ended and control subjects were offered the pneumococcal vaccine.

The last' component of the complete application was the manufacturing bridging study which was completed in May of this year. The meeting today is taking place about five months after receipt of the application.

Data from 11 different clinical studies were included in the application, studies 18, three and seven were early studies conducted among infants to demonstrate satisfactory safety and immunogenicity in preparation for the large safety and efficacy trial, which is trial 118-8. Clinical studies 118-12 and 16 served to demonstrate consistency of vaccine production and ability to scale up production as will be discussed.

Data from these additional studies were also included in the application. 92-5 was an early study of 5-valent conjugate vaccines, which direct saccharide dose and model selection. Study 18-2 is the only study of the vaccine in adults. Its objective was to demonstrate acceptable safety and immunogenicity in a small number of adults before proceeding to study the vaccine in infants.

Study 118-15 is an ongoing clinical efficacy trial conducted among Native American Navajo and Apache populations. Only immunogenicity data intended to support catch-up schedules was provided to the PLA, and in studies 124-2 and 124-501 provide data for a 9-valent pneumococcal conjugate vaccine intended to support vaccine compatibility in catch-up schedules.

Not included in the application are data addressing use of the vaccine among some high-risk populations, including children with sickle cell disease, HIV infection, and Hodgkins disease. Also not included in the application are data from a trial conducted in Finland, evaluating the effectiveness of the vaccine in preventing otitis media.

Clinical studies essential for regulatory approval were a large safety and efficacy study conducted at the northern California Kaiser Permanente

system, a lot consistency study 118-12, and the manufacturing bridging study, 118-16. These latter two studies are also important for the assessment of safety, as these are the only studies in the application conducted among infants which did not make use of the meningococcal c investigational vaccine in the control arm, thus allowing a more clear assessment of vaccine reactions.

Antigen content of the pneumococcal vaccine was presented earlier. Shown here is a comparison to the antigen content of the meningococcal c vaccine used as a control in the efficacy trial. Contents of the diphtheria toxoid carrier is similar. Total saccharide content was also similar, although the meningococcal vaccine contains oligosaccharide while most of the saccharide in the pneumococcal vaccine is polysaccharide.

Prevenar is a liquid formulation which is preservative free, and it does not contain thimerosal.

All data in the application supporting a claim of efficacy against invasive disease come from the northern California Kaiser Permanente trial. The original plan for the efficacy study had included interim looks at eight, 20 and 40 cases of invasive disease, with stopping rules for case splits at each

look. FDA did not recommend the early look after eight cases.

As the trial progressed, the sponsor requested a determination for a minimum number of cases, for which an interim analysis might be conducted with specific case splits leading to a termination of enrollment and a claim of efficacy. Agreement was reached in November of 1997 to modify the sequential analysis plan by eliminating the look at eight cases, and instead to provide for one interim analysis when 17 cases of invasive disease due to vaccine serotypes accrued among children who were vaccinated per protocol.

The test criterion at the interim analysis was specified as follows. If no more than two cases out of the 17 were observed in the vaccinated group, in the pneumococcal vaccine group, the vaccine was to be considered efficacious and the trial would be stopped for evidence of efficacy.

Enrollment into the efficacy trial was terminated in August of '98. At that time, nearly 38,000 infants had been randomized and received at least one dose of study vaccine. Exact follow-up times for all subjects were not available at the primary analysis. Follow-up times established in

April were used to project the estimated follow-up time for the August analysis. Variation of actual from projected follow-up time would not affect the vaccine efficacy estimate, but could alter the confidence intervals.

The sponsor and FDA have conducted supplementary analyses demonstrating that plausible ratios of follow-up times between the two vaccine groups at the August analysis would not vary substantially with additional data and, therefore, the confidence intervals would not change.

As you can see, about 7,500 randomized subjects were not included in the per protocol analysis, but were included in the intent to treat analysis. Reasons for exclusions from the per protocol analysis and protocol violations were provided as supplemental to the PLA. The most common reasons for exclusion were not receiving the third dose by the date of cutoff, and the third dose not given within the first year of life.

Children were also excluded for failure to receive study vaccines in the designated time frames, receipt of incorrect vaccines, failure to meet entry criteria, receipt of immunoglobulin, invasive disease and death. LOSS of health plan membership did not

result in exclusion from the per protocol follow,-up unless a dosing violation occurred.

The number of subjects appears to be well balanced between the study groups by reason of exclusion. The number of subjects randomized, as shown in this slide, differs from the number evaluated at the efficacy analysis seen in the previous slide, because the data cutoff for determining follow-up was the April 30th date, while the primary analysis took place four months later.

Doctor Black already presented the race and ethnicity study population. The vaccine groups appear to be well balanced with respect to race and ethnicity.

Results of primary analysis were previously shown. Results were remarkable. No cases of invasive disease due to vaccine serotype were observed. The vaccine efficacy estimate was 100 percent, and the lower bound, the 95 percent confidence interval, was 75 percent for the per protocol analysis and 82 percent for the intent to treat analysis.

Five cases of invasive disease had accrued in the control group among children who received one or two doses. Efficacy for one or two doses cannot be inferred, however, as the lower bound of the 95

percent confidence interval including zero. Between the third and fourth doses ten cases had accrued. This number of cases provided an estimate of the vaccine efficacy for the interval between after the third dose until the fourth dose, with a lower bound of the 95 percent confidence interval about 50 percent. Protection after three doses beyond 12 to 15 months cannot be inferred, because most subjects received a fourth dose of vaccine.

In FDA's review of the efficacy data, we sought to be assured that no cases of invasive disease may have been missed. A few missed cases in the pneumococcal vaccine group would have a large effect on the efficacy estimate and on the confidence intervals. To this end, we requested that all bacterial culture results for the study population at the time of the primary analysis be tabulated and reported. The final summary of all non-pneumococcal culture results revealed no imbalance across the two groups. All positive bacterial cultures were identified by genus and most were speciated. Thus, for subjects who remained in the Kaiser plan throughout the study, the likelihood that cases of invasive disease may have been missed is low.

Although not relevant to the regulatory

approval of Prevenar, it may be of interest to the committee that six meningococcal isolates were also identified, three in each vaccine group and none of the isolates was meningococcal type c.

Of the 22 cases of invasive disease in the control vaccine group, five were among partially vaccinated infants. All five were less than six months of age. One of the 17 cases among the older fully vaccinated subjects was hospitalized. Three of the infants less than six months were hospitalized. All cases were bacteremic. Bacteria were also isolated from the spinal fluid of two infants less than six months of age.

In addition to the two infants with meningitis, two children were diagnosed with sepsis. According to the case narratives provided, however, neither of these children were hospitalized. Thus, the diagnosis of clinical sepsis appears to be of little value in assessing severity of disease in this trial, and illustrates the desirability of having common diagnostic criteria.

None of the cases of invasive disease at the primary analysis occurred among immuno compromised individuals. There were no deaths. One infant with meningitis suffered residual hearing loss, all others

were said to have fully recovered and were doing well.

Well, in August of 1998, the enrollment ceased. Partially vaccinated subjects continued to complete the vaccine schedule, and follow-up of subjects was added to the continuing surveillance of efficacy outcomes and safety. An analysis of all invasive disease accrued through April 20th was provided with the PLA. Complete data sets including safety and calculations of follow-up time are not yet available for the extended surveillance period.

Vaccine efficacy data for cases through April of '99 are consistent with data in the primary analysis. One case of invasive disease due to vaccine serotype occurred among the fully vaccinated subjects, and 39 cases were observed in the control group. The one case of invasive disease due to vaccine serotype in the pneumococcal group presented no unusual characteristics. This child was two years old, Caucasian male, who received four doses of vaccine. Onset of illness was about one year after the fourth dose. He presented with low-grade fever and a right lower lobe pneumonia. Blood culture grew a serotype 19f, which is penicillin sensitive, and he recovered fully.

Two additional cases of invasive disease

occurred in the intent to treat population. A 12-1/2 month old African American female received one dose of vaccine, her illness was 317 days after the vaccine. Blood culture was positive for serotype 6b. She was treated out patient and had a full recovery. The other child was a 2-1/2 year old Caucasian male who was fully avccinated, but he was diagnosed with acute myelogenous leukemia, received a single round of chemotherapy and when he came in for the second round was discovered the bacteremic 570 days after the fourth dose. That serotype was 19f, which is penicillin resistant. He subsequently died, however, apparently not of pneumococcal disease, which was successfully treated.

In this table compiled from case narratives, characteristics of all 61 cases were broken down by whether the case was due to vaccine serotype or not. One case of invasive disease due to non-vaccine serotype did not have a positive blood culture, as Doctor Black mentioned, this was from, the pneumococcus was isolated from a thyroglossal duct cyst. Five cases of meningitis were due to vaccine serotype and one case to non-vaccine serotype, accounting for about ten percent of invasive diseases cases overall. Two children with invasive disease

were immunocompromised. the child with leukemia was discussed earlier. One child also had severe combined immunodeficiency disease in the control group, and he developed invasive disease to the non-vaccine serotype.

Four deaths occurred among the study population. Two of the deaths could be attributed to pneumococcal disease. Both were in the control group, an eight month old Caucasian female was diagnosed with pneumonia and meningitis, died due to complications of meningitis. The serotype 14 was isolated, it was relatively resistant to penicillin. It was isolated from both blood and spinal fluid, and there was no evidence that the child was Immunocompromised, and then a 28 month old Filipino make with a history of asthma was diagnosed with multiple lobe pneumonia and respiratory disease, serotype 19f drew from blood, which is penicillin sensitive. There's no history of prior corticosteroids or that the child was immunocompromised.

Penicillin susceptibilities of pneumococcal isolates in the trial were reported. Of vaccine serotype isolates, 15 percent were resistant and 21 percent had intermediate resistance to penicillin. One non-vaccine serotype case was penicillin

resistant, that was type 23a.

Well, nine cases of invasive disease due to non-vaccine serotypes had accrued at the follow-up, at the end of the extended follow-up period. This is only one additional case since the primary analysis in August. During the same period, 30 additional cases of vaccine serotype had accrued, thus replacement of vaccine serotype by non-vaccine serotype was not observed during the follow-up period of this trial.

Overall, of the 61 cases of invasive disease, 52, or 85 percent, were due to vaccine serotype.

Race and ethnicity were determined for all cases of invasive disease. Here I've put together the race and ethnicity of the various cases compared to the race and ethnicity in the representative sample seen earlier. While the confidence limits about these percentages are wide, it does appear that invasive disease cases were disproportionatelydistributedwith fewer Asians and more African Americans affected.

I'll now discuss safety. The bulk of the safety data does come from the efficacy study as well. Hospitalizations within 60 days, emergency visits within 30 days, out-patient clinic visits for seizures, allergic reactions and asthma were reported

in the PLA, also events resulting in study termination contributed to the ascertainment of adverse events. A randomly selected subset of infants were actively monitored for vaccine reactions through the use of diary cards and telephone interviews. The subset included about 7,500 infants who received whole cell pertussis vaccine and 1,500 who received acellular pertussis vaccine, and the same cohort was monitored for each vaccine dose.

When the efficacy study began, all children received whole cell vaccine with the primary series. This table shows that about 75 percent of subjects received whole cell vaccine with all three doses of the primary series, and 17 percent received acellular pertussis vaccine for all three doses. Various combinations were also possible.

Well, much of the vaccine reaction data has already been presented, most of it in graphic form, I'll present a few table showing data with statistical analysis and click through a number of slides. Local reactions were assessed pair wise between left and right legs of the same child, in order to compare pneumococcal vaccine to DTB Hib. Some children also received hepatitis B vaccine in the same leg as DTB Hib.

It was also possible to compare local reaction rates across study groups in order to compare pneumococcal and meningococcal reaction rates, and both sets of comparisons are shown on this slide. This is dose three of the whole cell pertussis with the primary series, erythema, induration and tenderness were more common for the whole cell Hib than for the pneumococcal conjugate. Rates of clinically significant reactions were also greater for DTB Hib than for the pneumococcal vaccine. In columns on the far right it can be seen that rates of local reactions and clinically significant local reactions were more common in the pneumococcal vaccine group than the meningococcal group.

Results after one and two doses are available and copies are provided to the committee. I'm just going to click through them right now. For those subjects who received acellular vaccines concurrently, Hib vaccine was administered in the same leg as the pneumococcal vaccine, and the worst of the reactions was reported. Hepatitis B vaccine, if administered, was inoculated into the same leg as DTaP and the worst reaction was recorded. Again, comparisons to both DTaP and the control vaccine are shown in this slide. After dose one, higher rates of

erythema, induration and tenderness interfering with limb motion were observed for the leg inoculated with the pneumococcal vaccine than for the DTaP, compared to the meningococcal group on the far right erythema and induration were greater in pneumococcal vaccine.

Tables for doses two and three are available to the committee, and copies of the slides. Local reaction rates of the pneumococcal injection sites were similar with each dose, but reaction rates for DTaP increased and comparisons were not statistically significant for the doses two and three.

At the fourth dose, erythema and induration were reportedmore frequently forpneumococcalvaccine than for DTaP. Subjects may have received mixed pertussis vaccines with the primary series, however, compared to the meningococcal vaccine clinically significant erythema, induration and tenderness were also more common with pneumococcal vaccine.

Data from the lot consistency study, 18-12, are presented to show a comparison between pneumococcal conjugate vaccine and Hib conjugate vaccine for local reactions. This comparison is possible because the control group in the study did not receive either pneumococcal or meningococcal vaccines.

Shown are local reaction rates after dose three, erythema, induration and tenderness were more common at the injection sites of pneumococcalvaccine. However, clinically significant reactions were uncommon. Similar differences in local reactions were observed with each dose in the primary series. Data for these doses are available to the committee in the briefing materials.

Summarizing local reactions, pneumococcal conjugate vaccine caused less local reactogenicity than whole cell pertussis Hib, but it appeared to cause more local reactions than DTaP, Hib conjugate and the investigational meningococcal vaccine. Except for erythema, no pattern of increasing local reactogenicity with sequential doses of pneumococcal vaccines was apparent in the primary series, and no data are available to compare pneumococcal vaccine to a fourth consecutive dose of DTaP.

In the efficacy study assessment of systemic reactions and adverse events attributable to pneumococcal conjugate vaccine is complicated by concurrent recommended immunizations and the use of the investigational meningococcal vaccine in the comparator group. Again, most of the data about systemic reactions have been shown previously

graphically. I will show a few tables with statistical analysis.

Shown here are data for dose one, using whole cell vaccine, whole cell pertussis, against a background of concurrently administered whole cell pertussis Hib. Fever and irritability were reported more frequently in the pneumococcal vaccine groups than the meningococcal vaccine group after reach dose in the primary series.

Rates of fever greater than 39 degrees in increased with subsequent doses, and were significantly more'frequent after doses two and three compared to the control group.

Other systemic reactions, such as prolonged crying, restless sleep, loss of appetite and vomiting, were also more common in the pneumococcal vaccine group for one or more doses in the primary series. Data for doses two and three are available in the briefing materials, I will show them briefly. This is dose one, dose two, and dose three.

Systemic reaction rates among infants who received acellular pertussis vaccine with the primary series are more likely to represent current practice in the U.S. Shown in this table are common systemic reactions after dose two, as this is the dose for

which systemic reactions were common. Fever was more common in the pneumococcal vaccine group after each dose in the primary series, but fever greater than 39 degrees shown here were more common after dose two. A loss of appetite occurred more frequently in the pneumococcal vaccine group after each dose, and that difference was significant after dose three.

Tables of systemic reactions for other doses are available in the briefing documents. I'll show them briefly. Dose one, and then dose three.

After dose four, when given concurrently with DTaP no significant differences between study groups were observed for fever or other systemic reactions. The fourth dose of acellular pertussis followed a primary series, though, in which most children received whole cell pertussis.

Data from the manufacturing bridging study are presented here, in order to compare a no-injection control all subjects received the acellular pertussis vaccine. One pilot lot and two manufacturing lots were pools for these comparisons. Systemic reactions were most prominent after dose two, and that's what is shown here. Fever, irritability, decreased appetite were more frequent in the pneumococcal vaccine group.

Data for doses and two and three are