hundred and twenty-eight were excluded from the data analysis. One hundred and ten because the subjects had not completed the three scheduled immunization visits where the subjects received the combination DTaP-PRP-T vaccine before the clinical hold, and 18 were excluded for these various other reasons listed here.

This left us with 228 subjects to be included in the data analysis.

Next.

Of the 228 subjects, 118 were male, 110, female. The ethnic background was evenly distributed amongst the sites, with the predominant race being Caucasian.

Next.

This shows the mean age of the subjects at each immunization visit, and as you can see, the subjects adhere quite closely to the age visit of the study design.

This first table shows the anti-PRP antibody responses stratified by the type of polio vaccine that the subject received. The mean anti-PRP antibody response in our OPV recipients was 3.2 -- excuse me -- 3.12 micrograms per mL, while our IPV recipients had a mean anti-PRP antibody response of

2.44. The difference was not significant between the two groups.

Ninety-five, point, two percent of the OPV recipients and 90.3 percent of the IPV recipients had an anti-PRP antibody response that was greater than 0.15. This was not significantly different.

Seventy-six, point, eight percent of the OPV recipients and 73.8 percent of the IPV recipients had an anti-PRP antibody response greater than 1.0. Again, this difference was not significant.

So we found no interference with the anti-PRP antibody response with the different types of polio immunization.

Next. Additionally, the type of polio immunization received did not influence the antibody response to anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, and anti-polio virus Serotype 3.

Our OPV recipients had a significantly higher anti-polio Serotypes 1 and 2 antibody response when compared to the IPV recipients.

Next slide.

This table shows the anti-PR -- excuse me -- anti-PRP antibody response stratified by geographical location, Chicago and New Orleans, and further stratified by the type of polio vaccine.

When we compared the OPV recipients from Chicago with the IPV recipients from Chicago, there was no significant difference in any of the parameters. When we compared the OPV recipients from New Orleans with the IPV recipients from New Orleans, there was no significant difference in any of the parameters.

We next compared the mean anti-PRP antibody response for the Chicago subjects with the mean anti-PRP antibody response of the New Orleans subjects, and as you can see, this was significantly different being that the Chicago subjects had a significantly mean anti-PRP antibody response at seven months of age compared to the New Orleans subjects.

Chicago subjects also had a significantly higher percent of subjects with an anti-PRP antibody response greater than 0.15 and greater than 1.0. We were quite surprised to find this geographical difference between the locations. So we next compared subjects who had received OPV from Chicago with those who had receive OPV from New Orleans, and again, the Chicago recipients had a significantly higher mean anti-PRP antibody response.

Likewise they had a significantly higher percent of subjects with an anti-PRP antibody response

greater than 0.15. The difference here was not significant.

When we compared the IPV recipients from Chicago with the IPV recipients from New Orleans, all comparisons were significantly greater in the Chicago subjects compared to the New Orleans subjects.

Next.

This table shows the anti-PRP antibody responses with the New Orleans further stratified data, further stratified into the two locations that had comprised the data set. When we compared the two locations in Louisiana, we found that the Metairie, Louisiana subjects had significantly higher antibody responses to all of the variables we calculated when compared to the Destrehan subjects.

When we compared the Chicago subjects with both Metairie and Destrehan, we found that the Chicago subjects had a significantly higher mean anti-PRP antibody response compared to Metairie and also compared to Destrehan.

The difference in the percent of subjects that had -- excuse me -- the difference in the percent of subjects who had an anti-PRP antibody response greater than 0.15 was not significantly different in the Chicago-Metairie comparison, but it was

significantly different in the Chicago-Destrehan combination.

Likewise for the percent of subjects with an anti-PRP antibody response greater than 1.0.

Next.

The mean antibody concentrations for all other vaccine antigens did not differ among the infants from Destrehan, Metairie, and Chicago with one exception. Anti-polio virus Serotype 1 was significantly lower for the Metairie infants compared to Chicago infants.

Next.

We were quite surprised to find the difference in geographical location, and we sat down and scratched our heads trying to come up with some answers. We interviewed both study coordinators, the study coordinator who had given the Chicago subjects their injections and the study coordinator from New Orleans who had given both New Orleans locations -- subjects at both the locations in New Orleans their injections, and we did this more than one.

And we found that there were no differences in the way the study coordinators handled the vaccines or the sera. There was no difference in the way they transported it to and from the sites.

We found there was no differences in the way they handled and mixed the vaccines prior to their administrating them.

We did have a problem during the study in that the refrigerator-freezer in New Orleans where the sera and the vaccines were kept, we noticed that it had for a short period of time, had a temperature that deviated one to three degrees Centigrade outside the optimum range.

As soon as we noticed it, we replaced the refrigerator-freezer and the vaccines, but this gave us our first possible difference as to the explanation why our New Orleans infants had lower anti-PRP antibody responses.

The second difference that we found were that the study coordinators had a difference in vaccine administration.

Next.

We felt that if the faulty refrigerator-freezer in New Orleans had produced the lower mean anti-PRP antibody responses in the New Orleans subjects, there would be a linear relationship between -- you can't hardly see it there -- the mean anti-PRP antibody response and the number of immunization visits for the subject received vaccines from the

faulty refrigerator-freezer, X0 being that the subject had no immunization visits where they received vaccines from the faulty refrigerator-freezer.

The number of parentheses is the number of subjects in each group, and as you can see, there was no linear relationship. Therefore, we felt that the difference, that the lower anti-PRP antibody levels in the New Orleans subjects was probably not likely due to the faulty refrigerator-freezer.

Next.

As I mentioned before, there were site differences in the way the two study coordinators did their injections. The Chicago study coordinator used a five-eighths inch, 25 gauge needle. She gave her injection at a 90 degree angle, and she tented the skin around the injection site before giving the injection.

The New Orleans study coordinator used a one inch needle, 23 gauge. She gave the injection at a 45 degree angle, and she left the skin flat around the injection site.

We reviewed the current literature to see if there was any indication that the difference in injection technique had produced the difference in immunogenicity, and we could find nothing to support

this.

And also, if you remember, just a couple of overheads ago I showed you that there was a significant difference between the two New Orleans locations. They were significantly different as far as their anti-PRP antibody response.

However, both locations received their vaccines from the same study coordinator.

Next.

We had 16 subjects who had an anti-PRP antibody response that was less than 0.15 micrograms per mL at seven months of age. Six of these were OPB recipients, ten IPV recipients. Fifteen received an additional dose of PRP-T. Three were from Chicago, five from Metairie, and seven from Destrehan.

Next please.

We currently have data on 12 of the subjects. However, one of the subjects did not have a pre-bleed done. So the pre-data are based on an N of 11. The mean antibody response prior to the additional dose of PRP was 0.04 micrograms per mL. Ten of the 11 subjects had undetectable antibody levels prior to the additional dose.

The mean anti-PRP antibody response after the additional dose was 5.24 micrograms per mL. After

the additional dose, all of the subjects had an anti-PRP antibody level that was greater than 0.15, and 11 of the 12 had an anti-PRP antibody level that was greater than 1.0. The one subject who failed to achieve this level had an anti-PRP antibody level of .3, and the subject was from Destrehan.

Next.

Based on the data I've shown you, we came to the following conclusions. One, concurrent IPV administration with the DTaP-PRP combination vaccine did not result in significant interference in this study.

Two, the mean anti-PRP antibody response was significantly lower for New Orleans infants compared with Chicago infants.

Next.

Three, the difference in the mean anti-PRP antibody response among sites does not appear to be caused by the faulty refrigerator-freezer or vaccine administration technique differences.

And four, 11 of 12 nonresponders had an anti-PRP antibody response greater than 1.0 micrograms per mL after an extra dose of PRP-T.

So why did we find different results than the Rennels group? Well, one of the reasons could

have been that we have a difference in study designs. Peggy's group gave a polio containing vaccine at two, four, and six months of age. We did not give a polio containing vaccine at six months of age. Therefore, the fact that we gave the DTaP-PRP-T combination alone at six months of age might have allowed it to overcome some of the interference that was present.

It is also possible that the different lots of the DTaP-PRP-T vaccine -- that the two studies used produced the difference in results, either by producing a difference in immunogenicity or by producing a different potential for interaction with other antigens.

And also it's possible that either one of the results were due to an alpha error. Now, could you go two -- not the next one, but two more. Don't put the next one, but put up the one after it.

And as far as the underpowered part, the anti-PRP antibody response for our IPV recipients was not significant. It did not test significant. Perhaps it was because the small sample size was under powered to declare this difference significant.

However, we calculated how many subjects we would have needed to find a significant difference between these two groups, and we would have needed to

enroll 809 subjects for this difference to be significant.

Okay. Can you go back to the overhead you had? No, the one before that.

And last, that some unknown factor caused the difference between the two studies, and now the last overhead.

I'd like to thank my colleagues at the University of Chicago, Department of Pediatrics, Vaccine Center for their support and help in this study, and also the private pediatric practices that contribute to their patients as subjects for this group, Child Life Group, Minor Medical Centers, Rothchild Oshner Pediatric Group, and Suniti Medical Corporation.

Thank you.

CHAIRMAN GREENBERG: Thank you, Dr. Zenko.

This is an interesting set of two studies. Can I ask one question first? Did the Rennels study also include Hepatitis B virus vaccine concurrent?

DR. RENNELS: No.

CHAIRMAN GREENBERG: So that's another difference. So it's conceivable that Hepatitis B virus suppresses the suppressive effect of --

(Laughter.)

CHAIRMAN GREENBERG: -- inactivated polio.

Okay. I'm sure there's lots of questions. I don't know how we're going to deal with them all. I'm going to have to limit them to some extent, but first Dixie.

DR. SNIDER: Thank you. I do think the absence of IPV at six months is potentially quite important, but I'm still really intrigued by the marked difference between Metairie and Destrehan, and I'm wondering in thinking about this further, since there was this same study coordinator, what else you've looked at. I mean the demographics. What other things have you examined and ruled out since you haven't been able to give us a reason for this marked difference between the two New Orleans sites?

DR. ZENKO: Well, we questioned the study coordinator. At first we thought there might have been a different ethnic background, and there wasn't any. In fact, she assured us that most Destrehan subjects were suburbanites just like the Metairie, in fact, had moved from Metairie to Destrehan.

So we just couldn't find any differences in the subject base between the two groups and the study coordinator could also not state that there was a difference, and she was very familiar with the

subjects.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: It would seem that there may be genetic differences between the Louisiana population and Chicago population, if only that Louisiana was settled by certain ethnic groups versus Chicago, which would have been more of a melting pot, and has there been any attempt to look at the genetics of these children to see if there are common denominators among the nonresponders or gross differences in the genetic make-up between Louisiana and Chicago?

DR. ZENKO: No. No, we haven't. And you have a good point. That is.

CHAIRMAN GREENBERG: Other questions?

DR. LEVINE: I have just an easy, simple one.

CHAIRMAN GREENBERG: Identify yourself.

DR. LEVINE: I'm Warren Levine.

I was just wondering if the faulty refrigerator -- which direction that faultiness went. Was it too hot or too cold?

DR. ZENKO: Too hot.

CHAIRMAN GREENBERG: Yeah. Too cold would be an unusual problem for a vaccine.

(Laughter.)

CHAIRMAN GREENBERG: Dr. Paradiso.

DR. PARADISO: Peter Paradiso.

I was just wondering. None of the studies, if I followed this right, had a DTaP-Hib given separately and IPV given separately, and so we don't know whether IPV affects the Hib when DTaP and Hib are given separately; is that correct?

DR. ZENKO: That's correct.

DR. PARADISO: And when the DTaPs were licensed, OPV was the standard of care. So that would have been the comparison of the interferons done. Do we know that with the introduction of IPV as the standard of care have we reduced the Hib responses? Has anybody looked at that particularly?

CHAIRMAN GREENBERG: So the question is basically just plain old Hib, is it affected. Is the response to that alone affected by IPV?

MR. PARADISO: Right, right.

CHAIRMAN GREENBERG: And is there somebody who has data to that point specifically? Please get up whoever has it, and it looks like we have two bits of data.

DR. BOSLEGO: John Boslego, Merck.

We have studies when Hib conjugate

vaccines are given with IPV and then separately. In other words, they're staggered, and those studies demonstrate there's no difference at all in the Hib responses.

DR. BOGAERTS: (Inaudible.)

CHAIRMAN GREENBERG: Could you get to the microphone and identify yourself?

DR. BOGAERTS: Hugues Bogaerts, SmithKline Beecham.

We subscribe that observation. We have made comparisons and there is no influence of IPV.

CHAIRMAN GREENBERG: Are there any other?

Dr. Faggett?

DR. FAGGETT: Yeah, just a question about carriage state of the patients in the Destrehan versus New Orleans. Do you have any information on that? Are disease incidences in those --

DR. ZENKO: I didn't hear.

DR. FAGGETT: Any difference in disease incidence in those populations?

DR. ZENKO: No, we haven't looked at that yet.

DR. FAGGETT: Okay.

CHAIRMAN GREENBERG: Dr. Daum and then Dr. Fleming.

DR. DAUM: I have a comment on one question that was raised from the panel, the question of Dr. Snider.

We also looked at transport of the vaccines. We looked at the interval between mixing the vaccines. We looked at the interval between mixing and vaccine administration. We looked at the type of syringe that was used. We looked at the time left on the bench before we interviewed them over and over again, even on tape. We have them on tape as to what they did at every single step of the way, and we could not detect anything that we could share with you this morning.

I also wanted to comment on someone else's question about Dr. Rennels' study. I guess it's a question perhaps Dr. Rennels might care to address, and that is that if the third dose of IPV that we did not give, in fact, is the item driving the interference that they found and we did not find at least in a significant way, then I would have expected Dr. Rennels' arms C and D to be different from each other because both of those groups were identical except one got IPV dose three at six months, and one got OPV dose one, which was polio containing vaccine dose three, if you'll follow me, at six months, and

they were not different at all.

Therefore, I don't agree that the third dose of IPP was the difference between our results.

CHAIRMAN GREENBERG: I'd just like to remind the audience, Dr. Daum obviously has lots of knowledge from this issue, but he had recused himself from this discussion previously. So I don't know how you're supposed to interpret that.

(Laughter.)

CHAIRMAN GREENBERG: But that's -- I'm not sure how you're supposed to interpret the data either.

Dr. Fleming had -- Dr. Fleming, before you, this is a computationally challenged question. Could all of this be numbers that we simply are seeing variability because nobody has enough power to really get the right answer and every one of the bits of data that we are seeing is simply scatter on the great experimental curve?

DR. FLEMING: Well, let me try to address that at least relative to what I was going to ask my question about. One of the issues that we were discussing at the end of your or you were discussing at the end of your presentation was the consistency between your results and the Rennels results, and actually I do view them to be consistent with

differences attributable to random variability.

Specifically, you seem to be addressing, in particular, the Arms B and D of the previous study, and what that previous study was looking at with Arm A was what was the impact when you compare Arms A and B for giving the separate rather than combination vaccines, and we saw a reduction from 98 to 94 in the percent of people who achieved at least .15.

And then when you -- and that was with OPV -- and then when you went to Arm D with IPV, it dropped down to about 85 percent. So your figures that compared 95 versus 90 actually are fairly consistent with the 94 versus 86 when you go to the most direct comparison with the Rennels results of Arms B and D, meaning that the two studies together are certainly giving evidence that there is a reduction in the percent that achieved .15 both by moving from separate vaccines to combination vaccines in combination with DTaP, but also in the presence of IPV over OPV there is further reduction, and the two studies seem to be quite consistent.

I don't have as clear a sense about the New Orleans versus Chicago factor because the differences there are fairly striking and are not as readily attributable to random variability.

CHAIRMAN GREENBERG: I'm going to have one more question or comment, and then we're going to move on to the open public session.

Dr. Stephens.

DR. STEPHENS: I'm still bothered by what I hear from the manufacturers and what I just heard regarding these two studies, and I'd like at least some comment from them about their impression of this interference or noninterference.

Anyone want to comment?

CHAIRMAN GREENBERG: This is specifically the interference of inactivated polio virus with -- okay.

DR. STEPHENS: Correct.

CHAIRMAN GREENBERG: So we have a question to manufacturers. Could somebody step up to this?

Dr. Calandra.

DR. CALANDRA: Aventis Pasteur was the sponsor of both studies. We agree with the conclusion that one cannot at this point ascribe why the difference occurred. We believe that the difference occurred.

We did not mention or I have not mentioned the Canadian studies. I refer to Pentacel earlier there. Over 1,300 children have been studied with the

IPV given concurrently, and we've not seen the interference which concurs with what the other two manufacturers have said.

So we cannot explain the isolated event other than to say it occurred.

CHAIRMAN GREENBERG: Identify yourself, please.

DR. HOWE: Barbara Howe from SmithKline Beecham.

I just want to clarify what study we have done to specifically look at U.S. licensed IPV and OPV when given simultaneously at separate sites with the Hib vaccine. We did a study in which DTPa-HEP-B (phonetic) was given at one site. It's a combination vaccine, Hib at a separate site, and the U.S. licensed IPV at a third site.

And then a separate group, this was compared to separate injections of DTPa, HEP-B at separate sites, Hib at a third site, and oral polio. That's U.S. licensed OPV, and the response, the anti-PRP response is that's the GMT's proportion greater than -- equal to .15 and the proportion greater than one microgram were comparable between the two groups, and it's with an N of about 100 per group.

CHAIRMAN GREENBERG: Thank you.

Any other questions?

Dr. Edwards.

DR. EDWARDS: I just wanted to comment that a number of years ago when we were looking at pertussis responses with Scott Halprin (phonetic) in Canada, we noted that some differences in the antibody responses to pertussis were noted in those children who had received pertussis vaccines in the presence of OPV versus the presence of IPV, and those were children who had received wholesale pertussis vaccine.

So I don't know. We had no answers either about the polio issue, but what another --

CHAIRMAN GREENBERG: That was also the same direction as this then.

DR. EDWARDS: That's exactly correct, yes.

CHAIRMAN GREENBERG: Okay. If there are no more questions, I'm going to now move on to the open public session, and we have at least two presentations. The first is by Dr. Eskola. I think I'm saying that correctly, and Dr. Eskola currently works for Aventis Pasteur, but is going to be presenting as I understand it data that was not obtained during that employment.

Dr. Eskola, what I would simply say is make your presentation as quick as possible so that

people have some time to get some lunch.

DR. ESKOLA: Thank you, Mr. Chairman, ladies and gentlemen.

I'm grateful for this opportunity to share our data and our views on the clinical impact on DTPa-Hib interference.

Before I go to my presentation, I really want to make it clear my current position. Dr. Frasch asked me in November to come to this meeting and speak on the Finnish experience with DTPa and Hib combination vaccines and also review briefly the statement and arguments and conclusions that were published in the Lancet in December about this topic.

While I conducted the studies in Finland, I was employed by the Finnish National Public Health Institute, and also when I worked as a member of the group elaborating this issue I worked for the Finnish National Public Health Institute.

However, on January 10th this year, I joined Aventis Pasteur so that now I'm employed by a vaccine manufacturer who is actively developing the combination vaccines, and I hope that the committee is fully aware of this potential conflict of interest.

Most part of my presentations I will speak on behalf of the group of six scientists who were

originally invited by SmithKline Beecham to help the company to explain the then new finding of interference between aceral (phonetic) pertussis containing DTP vaccine and Hib conjugate vaccine.

However, the group extended its work, and I understand we worked very independently for two years not only to try to explain the interference, but especially to elaborate the clinical impact on this interference and the results of this working group were published in the Lancet in December. The members of the working group are listed here and several of them are present in the audience today.

First I was asked to review briefly the Finnish experiences, and to just summarize the results, we first conducted a study with two doses of DTPa-Hib vaccines either separate injections or mixed, and we found that when the vaccines were given as a separate injection after primary immunizations, the antibody concentrations were five to tenfold higher than when the children received these two doses mixed, as mixed injections.

After the booster doses, you could see there's still a difference between the antibody concentrations, but the difference was not so remarkable, and in all groups the response was clearly

an animalistic type of response.

The working group I referred to first tried to figure out the mechanism of the interference, but we came to the conclusion that there was not enough data to conclude or to find out the mechanism. This was part of the data that we reviewed, and this is unpublished data, may be interesting to the committee from Finnish trials.

We gave these DTPa and Hib vaccines either as a separate injection in two legs, as a separate injection in the same leg, and the distance between the two injections was relatively small. It was about one inch, 2.5 centimeters, or then the third group received the vaccines as a mixed injection, and this group was the only one where we saw this interference so that these results to us that the mechanism at least in this case may be due to physical-chemical interference, but there may be also other explanations that we may come back later today in Dr. Insel's talk.

Okay. Then the main part of the working group's work was to clarify or at least our view on the clinical impact of this interference, and we started our work by analyzing the efficacy trials with Hib combination, Hib conjugate vaccines.

In this first slide, I had summarized the

efficacy trial results from the Finnish trials with PRBD or HbOC vaccine. The point estimate of the efficacy was 90 percent, from 87 to 95 percent, and we felt that at least the traditional threshold considered to be surrogates for protection. At least the threshold 1.1 -- 1.0 micrograms did not predict protection, and even if one predicts the protection on the basis of the antibody consideration, .15 micrograms per mL, the estimate would be such that a lower efficacy would be predicted on the basis of these concentrations.

Quite similar findings were derived from other studies. Here I have summarized the U.S. efficacy trials or the Alaskan trial with low efficacy to other efficacy trials with higher efficacy estimates, and the third slide about the efficacy trials or efficacy experience comes from the United Kingdom where the efficacy up to four years of age is high, and in spite of relatively low antibody concentrations and relatively low percentages of children above those traditional thresholds.

So our conclusion was that those thresholds were not so relevant with the conjugate vaccine as they used to be with the Hib polysaccharide vaccine.

This slide has already been shown today. We conducted an extensive literature review where we collected data from all immunogenicity studies with different Hib conjugate vaccines, and as was already pointed out today, the geometric mean concentrations in children receiving the combination vaccine were lower then the children receiving the vaccines as a separate injection.

But in general, these antibody concentrations were in the same range than with other licensed Hib conjugate vaccines.

And there seemed to be no effect after the combination of DTPa and Hib conjugate vaccines on the induction of immunologic memory or priming because children receiving the combination vaccine had clearly an anamnestic type, strong antibody response or high antibody concentrations. Likewise the children who had received priming with Haemophilus conjugates as a separate injection.

So that our conclusion was that at least in the combination vaccines the ability to induce immunologic priming was not affected.

These data were also briefly reviewed in the morning. We tried to find data speaking for the functional activity of the antibodies, and I have to

say that the evidence was not or the data was not too strong, but we found some pieces of evidence that as measured by the avidity of the antibodies or by the opsonic activity, there were no marked differences in the functional activity of the antibodies irrespective of whether the children had received the vaccines either as mixed or as a separate injections.

As was pointed out in the morning, there was a significant difference in the opsonic safety activity of the sera in these two groups, but when we took these OPAs in relation to the German mean concentration of the antibodies, there was no difference between the groups.

We also wanted to look at what kind of evidence there is about the induction of mucosal immunity, and there was quite little data on that.

One knew that usually there needs to be quite a high concentration of antibodies if one wants to have IgT antibodies on the mucosal membranes. One of the threshold values was three micrograms per mL that this has been reported in the literature.

Therefore, we felt that the lower antibody concentrations with the combined vaccines might make them less effective on mucosal membranes, and this may we something that needs to be considered while

decisions are made.

There was also quite a little evidence on the impact on mucosal carriage of Hib with DTPa-Hib combinations. We know that Hib polysaccharide generally did not reduce carriage and most Hib conjugate vaccines are able to reduce the carriage, but, however, as was reviewed earlier today, this experience in Alaska demonstrated that the close variance in high risk populations really is important.

There was no direct, no hard data on impact of DTPa-Hib combinations on carriage available to us.

We summarized in the review published in the Lancet our views like this. There is clearly an interference between components in most DTPa and Hib combinations. Anti-PRP concentrations after the combinations fall within the range achieved with licensed conjugates, and DTPa-Hib combinations seems able to induce immunologic memory and functional reactive antibodies on the basis of the data that was available to us.

On the basis of all of this review and thorough discussions, the group felt that there are several unanswered questions related to the mechanism of the interference impact on mucosal immunity and

herd immunity, and therefore, controlled and carefully monitored intraduction would be prudent.

However, the group felt that the benefits of the combination vaccines are greater than the negative aspects of these combinations and was ready to recommend and encourage the use of DTPa-Hib combinations.

Thank you.

CHAIRMAN GREENBERG: Thank you, Dr. Eskola.

Very few questions. Dr. Fleming.

DR. FLEMING: Just a very brief one. If we go back to your Finnish efficacy trial data, we've had a lot of discussion today about using the .15 as the surrogate, so to speak. It really looks like in that data set it failed as a surrogate.

Differences between the PRP-D and the Hb[illegible] of 68 and 100 percent who achieved that were as efficacy was 90 and 95 percent in those two groups. So it was very nonpredictive of actual --

DR. ESKOLA: Exactly. That was also a conclusion, that these thresholds were not so valid anymore with the Hib conjugate vaccines.

CHAIRMAN GREENBERG: In the audience. Step up to a microphone.

DR. POOLMAN: I'm Jan Poolman from SmithKline Beecham.

What I'm left out with with this morning's discussion, and also it's been demonstrated in Juhani's talk, is that we're quite a bit snowed under, is the difference between natural immunity and vaccine induced immunity, and these conjugate vaccines are doing better than nature.

And so what it means, that there is a distraction, particularly at pre-booster period of detectable antibody levels and protection even in the efficacy trials when herd immunity was not really in place, and it has been demonstrated by a number of authors that there is clearly antibody maturation going on after post primary up to pre-boost.

And so what I'm left over, also seeing the elegant data on children still having disease at low levels of antibodies, but that's on the basis of natural immunity, I do think that on the basis of evidence we have and affinity maturation being demonstrated, that particular at pre-boost period the .15 microgram antibody level may be an over estimation, and with vaccine in used antibodies at that particular time because of their better functionality, there may be a different correlate

there.

And I'd like to hear some comments about that, and just as a short comment on the functional activity of antibodies induced by combinations, we've done a couple of studies. I think Dr. Ferrieri also asked about the significance. These differences have never been significant.

CHAIRMAN GREENBERG: Can I just get a clarification? There's lots of questions, and we're not going to be able -- can you stay at the microphone for a second?

I'm confused. Antibody maturation, I saw no evidence of affinity maturation that is presented. I saw the evidence of inducement of rapid immune response, but the affinities, am I missing something here or --

DR. POOLMAN: I agree with you that the data presented this morning have not been showing that, but it's published by Dr. Pichichero, Dr. Goldblatt, Dr. Granoff, and we have also in our latest studies clearly demonstrated affinity maturation.

CHAIRMAN GREENBERG: So just so I understand that, are there functional assays of antibodies that demonstrate enhanced functionality after vaccination in some assay? I've seen no data

for that.

DR. POOLMAN: No, that's also correct, and the data that were shown here were post booster data. We have recently done -- looked at functionality on post primary and compared to post boost, and there's a clearly substantial increase in functional activity on an antibody weight basis.

Unfortunately at pre-boost level, the antibody levels are so low that the functional assays we have, opsonic (unintelligible) and bactericidal assay are too insensitive at that antibody level to demonstrate avidity, but the avidity pre-boost and post boost is basically the same. There's not much more affinity maturation because with the booster and the booster antibodies or antibody bake ways (phonetic) clearly have more function.

CHAIRMAN GREENBERG: Dr. Snider.

DR. SNIDER: Well, I'd just like to follow through with that. I mean, it seems to me that what is being hypothesized or stated is that the conjugate produces lower levels, but functionally better antibodies, but we haven't seen the data. The only data we've seen say there's no difference in the functionality, and we have also heard concern about levels of antibody and mucosal immunity and carriage.

And there's a disconnect here that I think you're trying to close, and I'm also trying to close with scientific data which doesn't seem to be being brought out thus far.

CHAIRMAN GREENBERG: I will go around. Dr. Granoff, are you going to be able to clarify this a teeny bit?

DR. GRANOFF: Well, yes. I mean, our laboratory has spent years studying antibody avidity and antibody functional activities, including the ability of antibody to activate complement mediated lysis, optimization, passive protection in animal models, and so we've really thought a lot about this question.

And as I listen to discussions on antibody function, although I have utmost respect for my Dr. Robbins, I do think that there are vast differences in antibody function that one sees in infants and older children, adults given polysaccharide vaccine and conjugate vaccines.

And one has very clear examples where the same amount of antibody on a quantitative basis measured in an antibody binding assay can have ten to 20 times different function in terms of the ability to passively protect the rat, and in general when you

control for isotype, its avidity is the marker of antibody function, and I would agree with Dr. Poolman that there are several groups that have looked at the avidity of antibody one month post vaccination, and then as the concentration declines into the second year, what they've shown is that there is an associated avidity maturation.

So the function of the antibodies present a year later on a microgram basis the function is actually better than one would predict at one month post. So just to summarize briefly, I think there are at least -- to predict antibody function and protection, there really are two variables. There's quantity and quality.

You can have equivalent protection with a poorly -- with a lot of antibody of poor quality or you could have low antibody concentrations and high quality, and you can get similar types of protection.

CHAIRMAN GREENBERG: I'm going to let this conversation go on a little bit because it's important, although you all may suffer hunger problems because of it.

I will simply say I agree. I hope that maybe this afternoon we'll see some data. That's what Dixie -- yes, Dr. Breiman.

DR. BREIMAN: Well, I guess my question is along the same lines. Could we, Dr. Eskola, overly assured by the data that you presented showing a reasonable efficacy despite a substantial proportion of people being below the .15 threshold, and I'm wondering if the difference between what we might be observing now versus what might have been observed pre-vaccine is a difference in microbiologic pressure that could affect efficacy.

And if one, given the data that you showed earlier or not the data, but the point that you made, that you need a pretty high systemic antibody level to give you a mucosal immunity, might we be sacrificing that if there was a universal sort of reduction of induction of systemic immunity?

DR. ESKOLA: Well, I think that there are really several situations to be considered here. First, our situation now is totally different from the pre-vaccination situation when the main thing was to protect individual children and the herd immunity effect became as a surprise and it was an additional benefit.

And now I think that I to a large extent agree with the discussion that George Siber had earlier this morning and these herd immunity effects

and individual vaccine failures may become more important questions throughout the discussion today.

CHAIRMAN GREENBERG: Dr. Siber and then Dr. Robbins.

DR. SIBER: Actually on Dr. Robbins' point, I just want to point out to you that the PRP-D study was done before vaccine was in universal use, and so one would have expected relatively minor herd immune effects in that study.

But I want to get back to a comment of Dr. Fleming's about the fact of the .15 microgram level does not really relate, is not really a correlative immunity.

I guess what you're looking for is that the efficacy percent matches the percent of individuals responding to that level and, in fact, is lower in the case of PRP-D. The percent responding was lower than the efficacy observed.

I wouldn't conclude there's no protective level. I would conclude then that the .15 is conservative. That's really lower than that.

And why is it conservative? It could be conservative for the classic debate we're having here between Dr. Robbins and others. The antibodiologists say it's the antibody that's important, and it's just

a lower level of antibody that could protect you.

The primers will say, "Well, for the conjugate vaccine even if you didn't respond to that primary series, we've been primed," and he'll make a good antibody response when you see polysaccharide later.

And I think that debate will go on. I think they're both correct. I think priming probably is important sometimes.

CHAIRMAN GREENBERG: Can I add a third? And Dr. Robbins is going to speak, but it seems to me the priming, George, and the level -- there was a third thing, which is the environment, and Dr. Robbins said that pressure is lower so that your risk is lower, and that's the part that has me most concerned because the environment can change in ways that we don't know.

And so I think what most of this panel has to decide with this, were all of a sudden the herd immunity that exists now to disappear, would we have a population that was at much greater risk as we lower this level?

And maybe John is going to say something about that, but that's in my mind what's going on here.

DR. ROBBINS: Just a small comment. Can I have the slide, please? I hope I have the right one. It's probably better than my interpretation.

(Laughter.)

DR. ROBBINS: We published this many years ago, but what it shows is that if you take Haemophilus influenza Type B, conjugate, which we call fluid, you see this is the antibody response, about 30 micrograms after one injection of two year olds. If this material is absorbed -- in this case we used a hydrogel -- the antibody response is remarkably diminished. In fact, when you take these absorbed vaccines, you cannot elute the polysaccharide from the aluminum under conditions you would have thought you would, that is, hot, three molar citric acid or EDTA does not remove it. It's essentially formed a stone, to be facetious. It's a multivalent binding between the phosphate and the Haemophilus and the aluminum.

Now, other aluminum adjuvants may not be as effective in removing the polysaccharide from solution, but I think that that's the major cause of what you're seeing because if you inject it separately and don't give a chance for that combination matrix to form, they work quite well.

It's when you mix them and they have a

chance to absorb that you reduce it. I think the aluminum is an important problem.

With respect to the quality of the antibody observed, I wouldn't want to prolong this. The level of .15, I think, is an estimate. It's a useful guide for predicting immunity on an individual basis. When you do a field trial and you inject large numbers of children, susceptibility changes because you've induced herd immunity, and the subjects are probably not exposed to the bacteria.

So interpretation of the relation between antibodies induced after vaccine and the effect of this is probably not valid.

I would like to give a personal opinion. I'm a little concerned about the apparent decline in levels of antibodies since these first studies were tried. I think after a primary series of the three major vaccines now, about a month later we got about ten micrograms, eight to ten micrograms per mL and then about 15 a month or 18 months later it went down to about one or two.

But now we're seeing levels of three micrograms after the primary series. Now, that may be enough. That may be enough. In fact, it may even be too much, but I think the note of caution is we can't

stop looking, and I just suggested looking in adults for disease because that might give you a quick clue that the herd immunity effect is waning with these low levels.

CHAIRMAN GREENBERG: Other -- Dr. Fleming.

DR. FLEMING: I think that coming back to the issue of the .15, certainly there is considerable evidence, considerable evidence that if we're looking at .15 as a measure of immunogenicity that will predict protection or predict efficacy, there's clearly a correlation. I mean the Finnish data are one example to indicate that there's more going on.

The concern that I'm struggling with is ultimately what is the question. The question I think that we will face is we have two approaches. We have combination vaccines versus separate administration. We have a situation now where there's an estimate of 99 percent protection on a population base. How much are we willing to back away from that?

We've had one prediction that for each percent you back away, when you go from 99 to 98, you're adding 90 cases of Hib disease. It's apparent to me at least from all this discussion that there are multiple factors going on that include the level of protection for the individual, and it's not clear that

.15. Maybe with the conjugate vaccines it's something lower than that, which isn't necessarily reassuring because I want to know what that lower level is, and then I want to find out if it's 99 percent with the separate vaccinations. Is it down to 90 percent with the combination? And we haven't seen data on that.

And then the other issue is the pressure. What is the impact of a different strategy using combination vaccines on the pressure, and another factor is in a disease such as this, a lot of the incidence occurs even before the third dose, and everything we're looking at is what's the relative immunogenicity after the third dose.

So I'm struggling with the basic question: how do we answer the FDA's issues here based on a surrogate. Point, one, five is certainly informative, but I'm convinced it's only a fraction of what we need to understand.

CHAIRMAN GREENBERG: I'm going to -- that's a very good summary, and I'm going to just add one little tidbit, and then I think we have one more person who wishes to speak, and that is I hope that somebody is going to address the advantages other than just simply saying it's better to give fewer vaccinations, but a clear understanding of the

advantages and how much they are worth versus the risks.

And I think that's a side of the equation that I'm not sure we're concentrating on as much. I realize that less injections is an advantage, but is it worth 90 cases, I mean?

CHAIRMAN GREENBERG: Dr. -- I'm going to say this wrong -- Pichichero. The hour is late, Can you make this really quick?

DR. PICHICHERO: I'm Mike Pichichero. I'm here on behalf of the Rochester NIH BTEU, although our site has numerous collaborations with all the vaccine manufacturers whose products have been discussed somewhat today.

I became a student of Hib disease in 1978 when I joined the discovery team of Smith and Anderson and Insel and have remained a student since. In 1985, it was our group who was among the first to put forward the notion about priming and to use PRP as an antigen to look at the issue of priming and memory.

And in '94 and '95, we participated in the first trials of DTaP-Hib combos and were among the first to observe this diminution.

Since that time we've continued to study the issue along with others. We would point out that

the major features of immunologic memory are priming as we see them are these four features, and the differences between the unprimed and absence of a memory response are shown on the transparency in comparison to the primed.

Memory response, our group and others have shown the DTaP-Hib combination by SmithKline Beecham produce IgG with boosts by both PRP or PRP conjugates; that the avidity is higher. Our group and Goldblatt's group have shown this from the U.K., that the antibody titres are higher. Our group, Goldblatt's group, Eskola's group, Dagan's group, and Frez Zepp and Heinz Schmitt's group has shown that data. And my brief presentation will focus on the kinetics.

In the study which Peggy Rennels described at the Rochester VTEU site, we were able to provide an amendment through our NIH contract to not only vaccinate these children with lowered responses following the DTaP-Hib combination, TriHIBit by Pasteur Merieux Connaught, but to look at the kinetics of the response when we gave them a PRPT booster.

Here are the pre-boost antibody levels. Of the 21 children who we studied, as you can see, two thirds of them have antibody levels below one.

When we looked at their antibody levels on

day three, we could not see any evidence for a rise in antibody by day three, but by day four-five, we were able to detect rises in antibody, and this clearly became the case on day seven and again on day ten to 14.

For the 21 vaccinees in this study, all of the children showed evidence of priming, and all had moderate to high levels of antibody.

Next transparency.

Dr. Siber mentioned his difference of opinion with mine and others that polysaccharides have a different kinetics for their memory responses than protein antigens. He made reference to some data which Dr. Dodson Madore of the same company kindly shared with me.

These are six children who were given HbOC vaccine at 18 to 23 months of age. You see their ages here, their pre-vaccine titres, their titres on day one, three, and here clear kinetic rises by day seven in these children.

The question would be whether these children are primed. In light of the natural priming, could these levels of .2 and so forth actually indicate that they are primed, and that with HbOC they are showing a response on day seven, which is fairly

consistent with our own observations.

Next slide.

We wanted to remind the audience of this data by Bob Daum published in '90. This was following the flurry of concern about a few cases of Hib disease which occurred in the immediate post vaccination period. Here we see the various vaccines in that study by Daum, and you'll notice that PRP at 24 months, there were 29 children, 20 of whom showed a decrease in antibody two to three days after the immunization, but seven showed an increase in antibody by day two to three, which would be suggestive of natural priming followed by a memory response.

The PRP OMPC at two months, one of four children had an increase two to three days after the vaccine, and by four months, four of ten children showed a measurable increase in antibody by day two to three, and if you look over here at the day seven data, the data would suggest to me that these children were primed in this group, this group, and this group.

Next slide.

CHAIRMAN GREENBERG: Michael, you've got a minute or two.

DR. PICHICHERO: Okay. These are data also which were shown in brief by Dr. Siber. This is

the data from Porter Anderson and myself which we are submitting.

Going back and looking at Boston's Children's Hospital in 1971 to '73, Dr. Anderson remembered that there were children who were admitted with Hib meningitis in these age groups who seemed to show antibody rises very early following contraction of their disease, suggesting that they were primed, but that their priming did not protect them from disease.

A few comments. Unconjugated PRP vaccine we recognize is preferred for study of memory and priming. Initial antigen complexing with antibody probably occurs and provides an under estimate of the antibody as we measure it post vaccine.

Quantitation of antibody at low concentrations is difficult, and even with any Hib conjugate vaccine, a few children will not respond.

Next.

I'm at the end, Harry.

Preexisting antibody does complex with Hib as a mechanism of inactivation and clearance. If the preexisting antibody becomes complexed before an immune response ensues through memory, then disease may occur, and preexisting antibody levels of .1

.15 in nonvaccinated children, as we've heard, is associated with protection.

My last one. We think the antibody quality -- we agree with Dan Granoff -- is very important that genetic predisposition of the host, as was mentioned by a committee member, is important and that inate immunity and immunologic maturity are risk factors in very young children, and so you cannot make leaps when you compare two month olds to seven month olds to 15 month olds, and so forth.

I have one more? That's it.

Thank you very much.

CHAIRMAN GREENBERG: Thank you.

I am going to call it quits now and give all of you 45 minutes for lunch. So you'll meet back here ten minutes later. The lunch room is reserved for panel members. So there's no excuse not to be back here at 1:30, and we're going to start sharply at 1:30.

(Whereupon, at 12:47 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

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

(1:34 p.m.)

CHAIRMAN GREENBERG: Okay. I hope you all have had a nourishing lunch, and I'd like to start off the afternoon with field experience with the Hib vaccine in high risk populations.

Dr. Jay Butler.

DR. BUTLER: Thank you.

CHAIRMAN GREENBERG: Again, all speakers, you'll get a gold star if you actually finish ahead of time.

(Laughter.)

DR. BUTLER: I'd like to use 20th Century technology. Could someone turn on the slide projector back there? Now if we could bring down the lights, thank you.

Already this morning we've touched several times on the experience with Hib disease among Alaska Natives, and what I'd like to do now is have a time to focus on the experience with conjugate Hib vaccines among Alaskan Natives.

In the pre-vaccine era, the rates of invasive Haemophilus influenza Type B disease among Alaskan Natives were among the highest that were documented anywhere in the world. The annual

incidence in the early 1980s among children age five years and less ranged from 400 to 600 cases per 100,000 per year.

This was a rate some five to tenfold higher than the rate observed in other parts of the United States. In addition to the high rates of disease, there were other aspects of the epidemiology of Hib disease in Native children which were unique. Disease tended to occur earlier, with nearly a quarter of cases occurring before age six months.

Additionally, some studies suggested that carriage may be slightly higher among Alaska Natives, as has been mentioned earlier, although these are not spectacularly higher rates of carriage.

Now, the CDC has conducted statewide laboratory-based surveillance for invasive Haemophilus disease since 1980. This bar graph shows the number of cases of invasive disease identified among Native children each year since 1980.

In September of 1991, universal immunization with PRP-OMP was instituted. Prior to the universal vaccination program, in general anywhere from 30 to even 60 cases of invasive disease occurred each year.

During each year from 1992 through '95,

only one to four cases occurred. In 1996, the Haemophilus vaccine for routine immunization was changed to HbOC combined with diphtheria, tetanus, and the whole cell pertussis in order to reduce the number of immunizations.

During the period from May 1996 through September of 1997, 16 cases of invasive Hib disease occurred.

Now, I will get these buttons straight before this talk is over.

Now, for several slides, I'd like to be able to present the epidemiology of Hib disease in terms of incidence of disease, cases per 100,000 persons less than age five years per year, and I'd like to present this in different time intervals.

The first is 1980 to '91, which I will call the pre-conjugate vaccine era, although this was a period when PRP was used. There was also a trial of PRP-D as you're aware.

1992 to '95 is the PRP-OMP era.

And then '96 to '97 is the HbOC-DTP era.

Rates of disease in all eras were much higher among Alaska Natives than among non-Native children living in Alaska. For both Natives and non-Natives there was a substantial reduction in rates of

disease during the PRP-OMP era, and this represents an effectiveness of roughly 95 percent in both Natives and non-Natives.

During '96 and '97, the increase in disease is reflected here and occurred exclusively among the Native population.

Now, this slide shows the area of residence for the 16 cases, and they occurred predominantly in the rural areas of the North Slope in the western part of the state. The urban areas of Anchorage, Fairbanks and Juneau are here in the central, south central, and southeastern parts of the state.

Now, this slide shows the incidence of disease in urban and rural areas of Alaska among Natives younger than age 5. Even in the pre-vaccine era, rates of disease were higher in rural areas. Both urban and rural areas enjoyed a substantial decrease in rates with the onset of the universal immunization policy with PRP-OMP.

The increase in disease which occurred in '96 and '97 occurred primarily among people in the rural areas of the state.

Now, I'm not a long time resident of Alaska, and I want to define a little more what we

mean by rural because I realize most people here have not lived in Alaska and many have not even visited yet.

When I say "rural," it may conjure these kind of agrarian images, but this is not what we're talking about.

(Laughter.)

DR. BUTLER: This is a more accurate picture. Villages of roughly 200 to 1,000 people, houses clustered together in remote parts of the state. Houses tend to be small. Families tend to be large. Most all villages have electricity, but most still do not have running water or flush toilets.

Public gathering places tend to be small, as you might surmise from the size of the Russian Orthodox Church, which was the largest public gathering place in this village.

The life style is primarily subsistence, and the weather can be harsh, the winters long. You know, this looks like the mall on Tuesday. This was as May morning in a village.

(Laughter.)

DR. BUTLER: Most of the villages are not accessible by road. Princess and Holland America don't take in places like this when they go to Alaska.

When the weather closes in several days may pass before planes arrive with supplies and groceries and take investigators back to Anchorage.

(Laughter.)

DR. BUTLER: The population is very young. The median age among Alaskan Natives is 17 years, and 25 percent of the Native population is younger than age ten years.

So in 1996 and '97, when the number of cases increase, a multi-faceted and really ongoing investigation was initiated which focused on the factors required for Hib disease to occur, and these factors were presumably the presence of susceptible children, which would be presumably due to low antibody levels, and also exposure to the organism which suggested that perhaps there were colonized persons in the community serving as the source of infection.

Now, the obvious question when we start talking about antibody level is is it possible these children simply were not immunized. This slide shows the distribution of Hib vaccination histories during the period of '92 to '95 when there were nine cases over a four year period versus '96 and '97 when 16 cases occurred. I'm going to say over a two year

period, although actually it was fairly focused within 15 months.

During the earlier period, the vast majority of children who developed Hib disease were unvaccinated. However, during '96 and '97, only one child was unvaccinated, and in fact, more than one third were under one year of age and had timely Hib vaccination with the combination product given as the first dose.

Now, in terms of antibody levels, I think it's worth stopping and going back and reviewing some data from about ten years ago. These are data from the late 1980s up through about 1990. It was a sequential, comparative study of immunogenicity of five different or really four different Hib vaccines, including two different preparations of PRP-T, with HbOC, PRP-D and PRP-T administered at two, four, and six months, PRP-OMP administered at two and four months. No booster dose was given.

Blood was collected before immunization at two months and then again at age four, six, seven, nine to 12, and 15 to 18 months.

As has been reported for other populations, PRP-OMP was the only vaccine which really led to a high increase, substantial increase in

antibody levels after a single dose.

However, the highest antibody levels were observed among children who had received three doses of HbOC. The decline in antibody levels over time were similar in each of the groups, although the levels seem to be most closely related to the peak levels after completion of the primary series.

Now, this slide shows the proportion of children achieving antibody levels of greater than or equal to .15 or greater than or equal to one. Among the purple bars reflect the children who got HbOC, the blue bars PRP-OMP.

Among the children who got one dose -- after one dose of PRP-OMP, nearly 90 percent had levels of .15 or greater. Three doses of HbOC were required to get these kind of levels when virtually 100 percent of children after three doses had levels of .15, and the declines are shown here.

Using the higher cutoff, no children achieved a level of one after one dose of HbOC. A little over half achieved it after one dose of OMP. However, after three doses of HbOC more than 90 percent had levels greater than one and more than half maintained these levels during the year after immunization, whereas the proportion maintaining these

levels who had received OMP was substantially lower.

Now, taken together, these data suggest that it is, indeed, very plausible that with a shift to HbOC as the primary immunization antigen, it's possible that there is a window of vulnerability here.

So the next question becomes where is the organism coming from. As it was stated earlier, regardless of antibody levels if children aren't exposed to the organism, they're not going to develop disease.

I'd like to describe three oropharyngeal carriage surveys. The first was conducted in Bethel, the regional hub of the Yukon-Kuskokwin Delta and five rural villages, including two which had experienced cases during '96 and '97. This occurred during the spring of '97. These were community based surveys, and it enrolled 496 Native children age one to five years.

Overall these numbers represent anywhere from 60 to 90 percent of all children living in the villages.

A second survey was conducted in urban Anchorage. Anchorage is a town of a little over a quarter million people. The living conditions are substantially different in Anchorage compared to rural

villages. This was conducted in late '97 and early '98. This was a clinic based survey, and it was conducted among 417 Natives, age one to eight years.

The final survey was in Barrow, where also cases had occurred. Barrow might be thought of as a village on steroids or a village after the impact of oil money. It has a population of roughly 5,000. This survey was conducted in September of '98. It was school and clinic based and enrolled 541 Natives and 160 non-Native children age one to 16.

Now, the next several slides will summarize each of those studies. The numerals for each age group represent the number of children who were swabbed. The height of the bars represents the proportion who are colonized.

In the Yukon-Kuskokwin Delta, 9.3 percent of children were colonized, and the proportion who are colonized by village range from 2.2 to 13.2 percent.

Taking all of the villages in Bethel together, the highest rates of colonization were among the children entering school with 14 percent of the five year olds having Hib recovered from their oral pharynx.

Now, all of these slides, to make them more comparable for you, have the Y axis set at 15

percent.

Now, the situation was very different in Anchorage where slightly less than one percent of children were colonized. In fact, only four of the 417 had Hib, and all of these were preschool age children, although the sample sizes for school age children were relatively small.

In Barrow, roughly four and a half percent of children were colonized, and this was true for both Natives and non-Natives. Although the colonization rates were similar, the distribution by age was a little different. Among Natives no children younger than five years were colonized, whereas the highest rates of colonization among non-Natives were in the preschool and early school age.

Among the Native groups, we saw colonization rates above five percent really going out until we were up into the teenage years.

Now, I should add, having described a little bit about the Native population -- say something about who the non-Natives are in Barrow. Roughly one-third of these people were of Asian descent, and indeed, four of the seven kids who carried Hib were Filipino. However, everyone who was colonized had received at least three doses of Hib

vaccine.

Now, this also leads to what is the vaccination coverage rates in this area for finding evidence of reduced herd immunity. The question is whether or not the herd is truly immune. This is data from the Alaska Native Health Service, as well as the State Health Department, showing the percent of kids who had received two doses of Hib vaccine by five months or three doses by 24 months, and this is from 1994 to 1998, and this slide shows the full range to really give you a feel for what the worst case scenario would be.

Coverage in rural areas ranged from 51 percent to 75 percent and was higher in urban areas. Again, coverage is defined by two doses by age five months, which is a fairly strict definition. However, in all areas basically 90 percent of more had received three doses of Hib by 24 months.

I'm told that there's more recent data from the National Immunization Survey for '97 and '98, showing that Alaska has rates that are now on par with national averages, and in fact, the rates among Natives are greater than that for the U.S. as a whole.

Additionally, I should point out that in the -- among the participants in the carriage surveys,

without exception, among children one to four years of age over 90 percent -- in fact, more than 94 percent had received three or more doses of a Hib vaccine.

So it's very difficult to attribute this finding to low vaccination rates.

So the conclusion of these investigations to date is that the convenience of combined diphtheria, tetanus, whole cell pertussis with HbOC had unexpected consequences for disease control among residents of rural Alaska villages. Differences in immunogenicity between PRP-OMP and HbOC were clinically significant in this population because of previously unrecognized colonization and ongoing transmission.

Additionally, I'll raise the question of whether or not at least for the youngest children the modest rates of on time immunization during the first six months of life may have played some role, although I would point out again the large number of children who develop disease who are completely age appropriately immunized.

The factors contributing to ongoing transmission in the face of a universal immunization program is unknown. It may well include the same factors that contributed to the high rates of disease

during the pre-vaccine era, such as household crowding and low socioeconomic status.

Additionally, it raises the question of whether or not there's some previously unidentified reservoir. The rates of carriage among school aged children in Barrow were surprising, and overall I would have to say our experience in Alaska has made us realize that we have to be very careful about looking at data from other parts of the world and making those assumptions for Alaska.

Next month we'll be returning to several of these villages and enrolling basically the entire community, including adults in these colonization studies.

And, finally, I raise the question of the role of the Hib vaccine used. We've had a number of discussions this morning about the role of priming and boosting for protection against invasive disease. I think those same questions need to be raised for protection against colonization and whether or not there may be differences among the Hib vaccines for natural and vaccine mediated boosting.

So what's happened since then? In late 1997, the routine immunization changed again to a sequential schedule giving PRP-OMP for the first dose,

followed by HbOC monovalent for subsequent doses. As you can see, the number of cases did reduce somewhat after this change.

This slide, again, returns to the rates of disease among urban and rural Natives younger than age five years, and as you can see, during '98, through the end of '99, rates dropped, but not to the same level as they had during the PRP-OMP era.

And there is some data comparing the immunogenicity of this sequential data to historical controls. I was not going to review that during the presentation, but the recently published data on that topic is included in your packet.

Now, if we look at the distribution of vaccine histories again, this data you saw earlier, again, there's a large proportion of children who are under one year of age and who are under immunized, and I'm defining "under immunized" as kids who received at least one dose of Hib vaccine and who are more than one month behind schedule for their next dose.

And I think it's notable that three of these six children were inadvertently given monovalent HbOC for the first dose. I realize there's a very small and denominatorless piece of data, but at least anecdotally it suggests that the problem in Alaska was

with the Hib antigen and not with the fact that it was included in a combination vaccine.

And I thank you for your attention, and I'm sure there will be questions, and I wanted to also acknowledge the people who actually did the work in getting this data together.

CHAIRMAN GREENBERG: Thank you, Dr. Butler.

We have time for just a few questions. Any questions here?

Dr. Edwards.

DR. EDWARDS: That was very nice, Jay.

I have a question about the fourth dose. Certainly there are very high rates of carriage in the older population. What is the coverage of a fourth dose, or were the children that were getting OMP -- did they get two doses and then a third dose at a later time or did they have fourth doses?

I guess booster doses in terms of carriage.

DR. BUTLER: You mean booster dose.

DR. EDWARDS: Right.

DR. BUTLER: At one time they were getting OMP and were just getting the two doses.

DR. EDWARDS: Right, right. I don't know

those data off the top of my head.

Orin, do you?

DR. LEVINE: No, I think that during the era when they were giving PRP-OMP for the primary series, they were getting the two doses at two and four months of age, and then they were getting a booster between 12 and 15 months of age, and the proportion of kids who were up to date by that regimen would be equivalent to what they were when they were getting three doses in the primary series and a booster.

So the coverage rates of primary plus a booster dose were very high.

DR. BUTLER: Or to put that another way, most of the data that shows the number of kids age 24 months who had received three doses is from the OMP era. So I think that's a reasonable surrogate to answer your question for the period up through the end of the routine use of OMP.

CHAIRMAN GREENBERG: Dr. Fleming.

DR. FLEMING: If the pressure remains in this community, which is, I know, an issue which is difficult to really sort through, could a clue for the doubling essentially in the incidence that occurred between '92-'95 and the '96-'97 associated with the

HbOC where the immune response seemed to be higher after a year, but it was discernably lower at four months and still lower at six months, and you had reported 25 percent of the incidence in this community as before six months.

Could that, in essence, be a major clue as to where the increase might be occurring?

DR. BUTLER: The increase in colonization?

DR. FLEMING: The increase in cases that occurred between the '92-'95 era and the '96-'97 era.

DR. BUTLER: I'm not sure I followed the question.

CHAIRMAN GREENBERG: I think Dr. Fleming is looking for a serologic correlate of the increased rate of cases in Alaskan Natives that was associated with the change in vaccine. Can you --

DR. BUTLER: Right. I mean that was the data I presented from the comparative study. I thought that was what you were making reference to initially. So it sounds like the answer to your question was in the question, if I'm understanding it correctly.

DR. FLEMING: The data that you had show earlier at the beginning of your presentation referred to the incidence of the 31 that occurred between '92

and '95, and then with the HbOC vaccine in '96-'97 there was the recurrence at a higher rate, and it was at about 60.

You also presented immunogenicity data for those two vaccines, and it appeared that the percent that achieved .15 was actually higher with the HbOC vaccine for children after one year of age, but it was discernably lower at -- very low at -- four months and low also at six, and given that there's a high incidence of disease, of Hib disease, in this community, 25 percent of the cases you noted occurred by six months, could the lack of an adequate immune response after the second dose and early after the third dose be causally inducing this increase?

DR. BUTLER: I think that's very likely.

CHAIRMAN GREENBERG: We have only a few --

DR. BUTLER: I hope that message came through in the presentation.

CHAIRMAN GREENBERG: We have only a few more questions. So please keep them very brief.

Dr. Estes.

DR. ESTES: I was struck by the apparent difference in age for the Native and non-Native children for carriage. Is it possible that there's repeated introduction of people coming in from Asian

for the non-Native population? And are they bringing in this organism?

DR. BUTLER: That's possible in Barrow. I think that's very unlikely in the more remote areas that were sampled in the first survey.

CHAIRMAN GREENBERG: Dr. Stephens, Dr. Ferrieri, and then Dr. Robbins, and that's it.

The carriage rates of non-Natives in Anchorage, do you have those data?

DR. BUTLER: No, we don't.

DR. FERRIERI: Ferrieri.

I gather that you don't have any serologic data from these patients, these cases.

DR. BUTLER: No, we don't, and we don't have serologic data yet from the carriage studies.

DR. FERRIERI: Thank you.

CHAIRMAN GREENBERG: Dr. Robbins.

DR. ROBBINS: Alaskan Eskimo children are also susceptible to other respiratory pathogens. Was there a change in the incidence of pneumococcal or meningococcal disease during this time?

DR. BUTLER: Not really. In fact, if anything, pneumococcal disease was a little bit down that year in '96 and back up in '97.

DR. ROBBINS: I notice that all of your

data for disease are in less than five year olds. Is there any data for over five year olds?

DR. BUTLER: Yes. You must know the answer to this question.

(Laughter.)

DR. BUTLER: There is. I mean there has been an analysis of adult disease that was mentioned earlier which showed a decline in rates of Hib disease in Alaskan Native adults, which was certainly temporally related with the reduction in the rates of Hib disease in young children.

It certainly would seem plausible that that's because of reduced colonization with Hib among the young children.

The survey data raises a bit of a conundrum as to whether that's true or not. We've gone back to the adult data to see if there's a difference between rural and urban adults and could not find any.

So, again, it's not clear to me why with the persistent colonization among young Alaskan Natives transmission seems to be occurring in somewhat selective situations.

CHAIRMAN GREENBERG: I'm going to end it there, except to ask a question myself.

I just want to follow up on Dr. Robbins' question. I think Dr. Robbins was saying that adults might serve as sentinels in the future if we change vaccines. We just had a circumstance here where a change in vaccine was associated with changes, it is felt, with children, and I think he was trying to get at does the sentinel theory work, that is, was there a rise in adults in that time frame.

DR. BUTLER: Yeah, and I think the answer to the question is at least in this population it does not work, although keep in mind the numbers are relatively small.

CHAIRMAN GREENBERG: And I would just like to push you a little bit, Dr. Butler. So the question before this committee is to consider changes in vaccines and what the risks are, and you just presented data on changes of vaccines that you are associating with elevated risk. Is that relevant to the question at hand or not?

DR. BUTLER: I think very much so. I mean even using the currently defined definitions for licensure, the differences between two different products had a big difference in terms of the clinical impact and the public health impact of changing vaccines.

So changing the criteria, I think, potentially at least for the Alaska Native population could be very problematic.

CHAIRMAN GREENBERG: Okay. The next speaker will be Dr. Heinz Schmitt, and he's going to talk to us about data from Germany.

And again, Dr. Schmitt.

DR. SCHMITT: Mr. Chairman, ladies and gentlemen, first of all, I'd like to thank the FDA to invite me to this meeting here and to present our data from Germany, which is a low Hib titre concentration country in a birth cohort of 800,000 children.

I was involved with DTaP-Hib combination vaccine since 1994, and we first presented these data in 1995 at ICAC, showing that the combination with DTaP and Hib vaccine in a mixed syringe leads to GMCs around 2.0 micrograms per mL, and this was similar with you combined DTaP with Hepatitis B, Hepatitis B-IPV and Hib. The titres here are between two and 2.6 micrograms per mL.

Now, 800,000 children per year get either this vaccine or this later vaccine, this five component vaccine, without actually HPV, and the uptake of DTaP-Hib combination vaccines is 90 percent in our country.

In this study, DTaP-Hib was given at a three, four, five schedule to prime children -- next slide -- and what you can see here is that the magnitude of the antibody response when a plain PRP was given is much higher than what is observed in unprimed children from published data.

Now, this has all been discussed this morning -- next slide -- and there are some -- I contribute some material for your briefing material. I want to concentrate on this unpublished study.

The rapid and high uptake of Hib combination vaccines in Germany prompted us to more closely follow the incidence of invasive Hib disease in our country.

I am the study coordinator, and Dr. von Kries from the University of Munich and Dr. Siedler and Dr. Niessing from the Robert Koch Institute at the Ministry of Health in Berlin are collaborators.

Now, the story of Hib vaccination in Germany is somewhat different from your experience in the United States. In '99, the PRP-D vaccine was the first to be licensed in our country with the two dose schedule and the booster in the second year of life. In 1992 only, other Hib vaccines were introduced.

Now, at this point I have to remind you of

a difference in the health care systems in our countries. In Germany, private pediatricians administer all vaccines available at no cost to each child, and they are free to choose among any of these vaccines once they were licensed, and they were all licensed in 1992.

In 1995, ACER (phonetic) pertussis vaccines were introduced with three dose schedule and a booster in the second year of life. November 1996, introduction of combined DTaP-Hib vaccines, and in January 1991, the DTaP-IPV-Hib vaccine, a five component vaccine, was introduced.

Next slide.

What we wanted to show is effectiveness of our vaccinations, and in order to calculate vaccine effectiveness, you need to know about the frequency of invasive Haemophilus influenza Type B disease. You need to know vaccination history of cases, and you need to know vaccine coverage in your population, and I'm going to show you how we got these data in the next couple of slides.

First of all, this was a population based survey of invasive H. influenza disease with active follow-up of reported cases. The reporting was done by ESPED, which stands for Surveillance Unit for Rare

Pediatric Disease in Germany, and it has a clinical arm and a laboratory arm, which work independently, and I will show you that in a minute.

The case definition of an invasive H. influenza disease was compatible disease in a child and isolation of the bacterium from a normally sterile body site.

Now, the laboratory ESPED -- the clinical ESPED system is based at pediatric departments. Surveys solicits the incidence of up to 12 rare diseases. It was established in 1992, and it works under the auspices of the German Pediatric Society, and report cards are sent monthly to all 485 pediatric departments in 416 hospitals nationwide.

And I have to say here another important information. There's this strict separation in Germany between children in private practice and children in hospitals. They have totally different doctors. So once you have suspected Hib disease, you automatically go to a hospital. You would never see a pediatrician. If so, he would send you to a hospital and the doctors are different.

Follow-up was done with a questionnaire in case there was a report of invasive Hib disease. Now the laboratory ESPED system works at the Robert Koch

Institute at the Germany Ministry of Health in Berlin. It was established in 1997. H. flu was introduced in 1998, and again, postcards are sent monthly to all microbiology laboratories nationwide which are 303 altogether.

Now, this is a map showing each dot, a clinic and laboratories involved, and you can see that they are scattered all over the country. There is no unexpected clustering there.

The response rate for postcards in both systems is above 94 percent, and the return rate for questionnaires, where we ask for additional questions on the case, is above 98 percent.

Now, how did we get the vaccination status of children?

In clinical ESPED, we called the pediatrician. We first of all looked at the questionnaire that we sent out, and if this didn't help, we got calls to the vaccinating physician.

Laboratory ESPED got vaccination history by telephone follow-ups done by the Robert Koch Institute to pediatric departments and/or to office pediatricians and/or to parents.

And actually I can say at this point we got vaccination card copies of all children who were

cases.

Now, how did we come up with vaccination coverage data? We had a random digit dialing telephone survey done by a professional organization which is Infratest in Munich. The vaccination history of 600 children eligible to have received at least one dose of Hib containing DTaP combination was to be documented, and actually it were 668 in the end, to give a precision of five to ten percent for the vaccination coverage with single vaccines.

Ascertainment of the vaccination status inclusive of brand names was done through interview of parents, copies of the vaccination certificate and also in cases, interview of the pediatrician.

Now, what are the results? These are the results for the vaccination status of age eligible children. Age eligible children is an important definition in this study. It means a child was born in a time frame so that it could have received a DTaP-Hib combination vaccine.

What you can see here, over the whole three years or in this study period, 55.5 percent of children had received a SmithKline Beecham DTaP-Hib combination vaccine. Three, point, six percent had received the Pasteur Merieux MSD, five component Hib

combination vaccine, and actually the second most common single vaccine used in Germany is PRP-D with five percent, and the others are shown here in this slide.

Next slide.

Now, we do know the vaccination status of children with single vaccines by the age of 12 months. For Infanrix-Hib combinations, zero dose was 1.9 percent. That means children receive the first dose of Hib vaccine in the second year of life. One dose, three percent; two doses, 24 percent; and three doses, around 70 percent.

For PRP-D these numbers are 2.7, 5.4, and 70 percent for the recommended two dose schedule of this vaccine.

Now, these are data from the clinical ESPED only. We probably had something between 1,200 and 1,600 cases of invasive Haemophilus influenza B disease prior to the introduction of Hib vaccination. Hib was licensed in 1991 as PRP-D. Hib was introduced into the ESPED system as one of the first rare diseases we studied, and in 1993 we had 120 cases.

And this went down to 54 in 1995. In 1996, then combination vaccines were introduced, and in 1998 we followed up with clinical ESPED, and we had

30 and 13 cases in the first six months of last year.

So you see a continuous decline of invasive Hib diseases since the introduction of combined vaccines.

Now, I have to give you the total number of cases we observed was 74, and that actually comes down to a number of 1.1 per 100,000 children to the age of five years. So that's the incidence per year.

We had 36 cases, Type B, 20 not typed, and 18 typed not B.

Now, 13 children were too young to have received any DTaP-Hib combination vaccine, and some were too old to have received any DTaP-Hib combination of vaccines, and we have to eliminate these from these numbers. So we have 24 children and eight children in the not typed group and five in the not typed B group.

Now, actually ten of these 24 children had received a DTPa-Hib combination vaccines, and 14 had received no vaccine.

So as the Chairman of the German Vaccination Advisory Committee, I worry about these 14 and not so much about these ten, and I will show you more data on these ten now.

Now, this is a busy slide, and I'll walk through it slowly.

One child had received Infanrix-Hib combination vaccine, one dose at age four months, and it got the disease at five months.

Four children had received a DTa or had received a Hib-PRP-D vaccine with different brand names mentioned here with two doses as recommended, and they came down with a disease later on as shown here.

One child had received Hib titre, two doses. Three children had received Infanrix-Hib at the time shown here, and they came down with a disease as shown here.

One child had received three doses of Infanrix-Hib, and it got disease at age 17 months. There was no case in any child who had received four doses of a Hib combination vaccine in our country.

Fourteen children had received no vaccine at all, and if you look at this table, 19 of these 24 children were not vaccinated or under vaccinated, and that is the problem, I think, in many populations, and the potential of having one percent less efficacy, I guess, is by far outweighed if you have a well effective vaccine, and if you can do something about these children who don't get their vaccines or don't get them on time.

Next slide.

Now, we do know the proportion of children which were vaccinated with a given vaccine. We know the proportion of children or of cases vaccinated, and with this formula published by Dr. Orinstein (phonetic) we can calculate vaccine efficacy.

Next slide.

One dose of DTaP-Hib or DTaP-IPV-Hib combination vaccine had a vaccine efficacy of 82.5 percent. Two doses had a vaccine efficacy of 93.6 percent, and with the PRP-D it was 70.4 percent only.

Also, if you look at the lower end of the 95 percent confidence interval, it's 89 here, and the upper end of the interval is 83.6 here. So there is a huge difference between them.

Somebody asked the question this morning what's the difference between one and two -- between two and three doses. Actually it's six percent, and I think it's very important to get this third dose, and if a combination of vaccines help to accomplish this, this may by far outweigh the potential risk of one percent less efficacy.

If you look at any child who had received at least one DTaP-Hib combination vaccine, vaccine efficacy was 97.4 percent.

Now, the first question that will come to your mind is were cases complete. Did we lose any cases or not find them?

We had two independent sources reporting to two independent institutions. So we could do a two source capture/recapture technique to look for cases we have missed, and theoretically, we have missed nine cases.

Capture/recapture came up with 83, and we found 74. If you assume that like with the other population with a 74 two-thirds of cases are Hib actually, then there would be six additional cases that we would have missed.

And assuming that all of these six cases would have received DTaP-Hib combination vaccine, vaccine efficacy would still be at 94.8 percent.

Now, how about other biases? I spoke about case ascertainment. Under reporting of vaccinated cases is highly unlikely because the reporting physician is different from the vaccinating physician. This is out patient, non-hospital doctor. This is always the hospital doctor.

Misclassification of vaccination service is impossible. We do have copies of all vaccination cards.

Estimation of coverage, we did a sensitivity analysis. Even if you assume that the number of unvaccinated cases was twice as high as we had calculated, then vaccine efficacy still would be 98 percent.

Now, also you might worry about the proportion of Type B cases in the not typed cases. If all untyped cases were Type B, then vaccine efficacy would still be the same because none of these untyped cases had really received three doses of a DTaP-Hib combination vaccine.

And this brings me to my conclusions. I think we have a reliable reporting system, which is ESPED. We see with the use of DTaP-Hib combination vaccines a continued decline of invasive H. flu disease in Germany. The field effectiveness for three doses of combination vaccines was 99.3 percent, and thus I conclude that for our country the lower antibody response to combined vaccines is not clinically significant, and the potential or hypothetical risk that one percent less efficacy might be due to the combinations I cannot see this from the data I presented, but other benefits are less injections, less visits to doctors, reduced costs, and very important, no delay in the busy immunization

schedule since other vaccines are coming up, and I think at least in Germany parents wouldn't accept five vaccines given at one well baby visit.

Thank you very much.

CHAIRMAN GREENBERG: Thank you, Dr. Schmitt.

We have time for just a few questions. Dr. Kohl.

DR. KOHL: What is the age distribution of Haemophilus disease in Germany? Is it more like the Finnish distribution or is it like the --

DR. SCHMITT: I have a slide with me now. I have a slide with me and can show you the actual data.

The peak incidence is after the first year of life. There's a peak very early, before children can get vaccinated, and then there is one in the second year of life. I have the age distribution, and I can give you the exactly data if you want to.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: Do you have any data on carriage rates in your population?

DR. SCHMITT: No.

CHAIRMAN GREENBERG: Any other questions?

DR. LEVINE: I wonder --

CHAIRMAN GREENBERG: Identify yourself, please, Dr. Levine.

DR. LEVINE: Sorry. Orin Levine.

I wonder if you could just clarify for me again what your overall immunization coverage rate was.

DR. SCHMITT: Yeah, there was that one -- yeah, I mean, it depends on how you look, and which method you look. What is for you overall vaccination coverage?

I showed you that one slide. This is actually slide number --

DR. LEVINE: Just what proportion of kids got --

DR. SCHMITT: Three, point, seven percent were not vaccinated.

DR. LEVINE: With even a single dose.

DR. SCHMITT: With a vaccine.

DR. LEVINE: Okay.

DR. SCHMITT: Fifty-five had received DTaP-Hib combination with these plus .6 from a different manufacturer who had just low coverage. So it's about 60 percent had received a Hib combination vaccine.

DR. LEVINE: Okay.

CHAIRMAN GREENBERG: Okay?

DR. FAGGETT: Harry, one question.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: Does the hospital physician refer the patient back to the community physician in terms of communication?

DR. SCHMITT: I guess what usually happens is they just write letters. Once the patient is discharged you get a letter indicating what happened. It's unusual that you call the treating -- the non-hospital based physician who delivered the vaccine.

DR. FAGGETT: Okay.

DR. SCHMITT: I mean, I'm working in a hospital, a university hospital, and I never call pediatricians outside. We don't have affiliations. It's a totally different system.

DR. FAGGETT: So you don't have the primary care provider set-up. Okay.

CHAIRMAN GREENBERG: Dr. Frasch.

DR. FRASCH: A clarification. In Germany, do the children receive a booster dose in the second year of life?

DR. SCHMITT: Yes, but since we had no case after fourth dose, we didn't -- I mean this is 100 percent, but there's nothing we can calculate

here. So we don't have this. It's recommended to give a fourth dose, but there was no case.

CHAIRMAN GREENBERG: If there are no other questions, we'll move on to Dr. Paul Heath, who's going to talk to us about Hib disease in the U.K.

DR. HEATH: Good afternoon, ladies and gentlemen. Thank you for the invitation to present data from the United Kingdom on our Hib vaccination program, and I hope that these data may be of assistance in your deliberations today.

First slide, please.

By way of introduction, as we've heard this morning, the current serological correlates of protection against Hib disease are derived from a variety of studies in unvaccinated populations, studies of passive immunization, and populations vaccinated with the plain polysaccharide vaccine, and the question that's being addressed is whether or not these correlates are relevant in the context of the conjugate vaccines.

And amongst the issues to consider, the evidence from the PRP-D experience of efficacy and effectiveness despite low antibody levels, the data we've heard about the quality of antibody post conjugate vaccine, and also the field efficacy of

conjugate vaccines other than PRP-D, and so I'm going to present data on the field efficacy of predominantly PRP-T, but also HbOC in the U.K.

If I had to summarize the experience in the U.K., it would be that we have a vaccine schedule which is completed early at two, three, four months of age at no booster dose and as a result, our anti-PRP antibody concentrations through the first five years of life are relatively low.

Yet despite this, we have a vaccine program which has resulted in a rapid decline in the incidence of Hib disease, a decline in Hib carriage, and clinical protection until at least preschool age.

In more detail, the antibody that we've seen in the United Kingdom is shown here. These are the U.K. published studies of conjugate vaccines, either PRP-T or HbOC given at two, three, four months of age.

And you can see that there are a variety of studies here, but generally one month after three doses at five months of age the geometric mean concentration is somewhere between three and six.

Two studies have followed antibodies through to 12 months of age and shown the expected decline, and then we followed a cohort of children

through until six years of age, and you can see that there is a further decline through until six, and this is about .5 micrograms per mL.

Next slide.

In terms of the correlates of protection, here are the proportions greater than or equal to .15 micrograms per mL in two studies, the Oxford studies and studies by David Goldblatt, who's here in the audience.

After three doses nearly 100 percent of children have a portion above .15. This is declined 60 percent in this study. Ninety percent in this study have levels above .15 at 12 months of age, and then a further decline about 60 to 70 percent above .15 at six years of age.

However, if we look at the proportions above one microgram per mL, after three doses it's around 90 percent. Then there is a significant decline so that out here we have anywhere between 30 and 50 percent greater than or equal to one microgram per mL.

On that background, the U.K. Hib vaccination program. Well, this began in October 1992. Two Hib conjugate vaccines have been used, PRP-T for children under the age of 12 months, and HbOC

for children over the age of 12 months.

The primary vaccination schedule I've alluded to. There was a catch-up component for the first year of the program from '92 to '93 in which children between the ages of 12 and 48 months of age were offered vaccine, and they were offered one dose if they were 12 to 48 months of age, and if they were less than 12 months of age, they had three doses.

The vaccine coverage over the eight years or so since the introduction of the vaccine has been high. Ninety-two to 94 percent have achieved -- have received three doses by 12 months of age with a small increment to 92 to 96 percent having received three doses by 24 months of age.

In terms of surveillance for Haemophilus influenza disease, there are two major components via pediatricians and via microbiologists, via pediatricians through the British Pediatric Surveillance Unit, a similar system to that described in Germany.

This is a system in which all pediatricians in the United Kingdom receive a card every month on which are listed a number of rare pediatric conditions, and there are asked to indicate whether they have seen such condition in the previous

month. They tick the box, send the card back. If they've seen no cases of any of the conditions, they tick the "no case seen" box and send the card back. So the cards are send back regardless of whether they've seen a case.

The case definition from the start of the routine vaccine program in October 1992 was for them to report Haemophilus influenza disease occurring in any vaccinated child, and we extended this in November 1995 to include Haemophilus influenza in all children regardless of vaccine status.

The second component of surveillance is via microbiologists and public health physicians, and they notify cases and send isolates to the National Haemophilus Reference Unit in Oxford, and they do so for all Haemophilus influenza regardless of whether the child is vaccinated or not.

You're familiar with these sorts of graphs. This simply shows the laboratory reports in England and Wales since vaccination began here in October 1992 in the different age groups. The light purple line is children one to four. This is children less than one year of age, and the dramatic decline that we and others have seen.

This shows the same figures, but for older

children and adults. So individuals five to 14 and individuals over the age of 15,a nd clearly these are individuals who have not be vaccinated and, thus, demonstrate herd immunity.

In terms of incidents, pre-vaccination we had an incidence of around 30 per 100,000 per year less than five. This fairly rapidly declined, and in 1998 the incidence of Hib disease was .6 of 100,000 per year in children less than five.

As another example of Herd immunity, since November 1995, as I mentioned, we've been capturing all cases regardless of vaccine status. I had the opportunity to look at the incidence in unvaccinated children. This is pre-vaccination, and this is post vaccination, and clearly the incidence in unvaccinated children less than 12 months of age is much, much lower than it was in the pre-vaccine era. Thus, these children are being protected by herd immunity.

Now, I think you'll have this. Many of you at least will have this table with you, which is good because it's very hard to see from wherever you are. This is the comparison between the incidence, the age specific incidence pre-vaccination, and this comes from an enhanced surveillance program in the Oxford region over six years before vaccination began.

This is the age specific incidence by year of age.

Here we have the numbers of cases of vaccine failures. So these are children who have received three doses of Hib conjugate vaccine, yet despite this developed invasive Hib disease, and again by age at which they developed Hib disease. So 96 cases over this nearly seven years.

And based on the comparison between the incidences from the pre-vaccine to the post vaccine era, we can calculate the vaccine efficacy or, more exactly, the vaccine effectiveness.

The figures show that the vaccine efficacy in the first year of life is very high, 99.4 percent, with very tight, 99 percent confidence intervals, and it remains high out through and including the sixth year of life. Here we have 97.3 percent, but the confidence intervals here are wider at 79 to 99 percent.

In fact, if we compare the first year with the subsequent years combined, there is a small, but statistically significant decline in vaccine efficacy from 99.4 to 97.6 percent, but as you can see, the actual efficacy out here to six years of age remains very high.

If I take the liberty of comparing the

data on antibody with that from clinical protection and compare the clinical protection up here from the surveillance study with the proportions protected by using the classic serological correlates of protection, you can see that those greater than predicted by those who have an antibody level above .15 micrograms per mL is certainly closer to clinical protection than that of the one microgram per mL level.

Indeed, this, too, is a conservative estimate of prediction as it's higher than this, particularly out towards five and six years of age.

Now, if our ascertainment through our surveillance is not as good as I think it is; in fact, if there were twice as many vaccine failures in the U.K. as those that we've captured, it makes very little difference. So that's this dotted graph or line here. So, in fact, the same conclusion applies.

I mentioned the decline in Hib carriage in the United Kingdom. These are studies performed by the Public Health Laboratory Service, children age one to 48 months of age. They did a study in '92, '94, and '96, and the data here are provisional in that these may be nought or one.

But clearly, there has been a significant

decline in carriage in this age group over the period of the vaccine program.

This looks at the same thing in a slightly older group of children, children 52, 54 months of age. This was done in '91, and this in the same time of year in '95, using the same methods, and again, a statistically significant decline in Hib carriage in this age group with no difference in carriage of Serotypes E and F as one would predict.

Now, why is there this difference between clinical protection and antibody levels? Well, immunological memory had been discussed and is clearly important. David Goldblatt here demonstrates immunological memory at at least 13 months of age or 12 months of age, these data you saw earlier falling to this level here of about .4, I think, but this huge increase in antibody in these children who receive a booster dose at 12 months of age, clear evidence that these children have been primed.

This is in the younger age group.

We've addressed a similar question, but in older children, three and a half and four and a half years of age. In this study there were 160 children and eight percent of them had undetectable antibody level. At least it was less than .15. They were all

given plain polysaccharide. They all had blood taken at a meeting of 23 days after the booster, and all responded. All had antibody levels greater than two. The geometric mean was 8.8, and the median-fold increase was 52.

But there were several who had very, very large increases, one of 390. Now, the obvious question is what would be the response in unvaccinated children in this age group, and we don't have that data from the U.K. There were very few unvaccinated children in Oxford.

In fact, looking through published data, I find it very hard to find a similar age group. There is Makela from Finland back here in 1977 looked at a similar age group, 51. These children had antibody prior to receiving the PRP booster, and they had a 23-fold increase. That's just demonstrated here.

So these are our children here, with these two showing very, very large increases, and the rest around just under ten or six to ten, and perhaps similar to that in this group who had not, who were unprimed, unprimed in the sense that they had not received the conjugate vaccine, but they did have some antibody, and clearly this was done at a time in

Finland when there was Hib circulating. So maybe they were primed.

So this comparison, I think, is difficult. So whether or not these children are having immunological memory I think is a moot point. I think these two certainly do.

In this same study, we also looked at carriage, and these children were followed over 12 months. They had three monthly swabs, and five children carried Hib over this 12 month period, and you can see that those children who carried Hib were boosted, had asymptomatic boosting of the Hib antibody levels. It was clearly significantly higher than those children who did not encounter Hib over that 12 month period.

Of interest, two of the five carried between the two blood samples that were taken, and they had very large increases in their Hib antibody level, again, I think, demonstrating that these children were primed.

So I'd like to conclude that in the United Kingdom vaccination with the Hib conjugate vaccines have resulted in a rapid and dramatic decline in both Hib disease and Hib infection or carriage, and this has been achieved in a vaccine program which results

in the persistence of low anti-PRP antibody concentrations, at least low by the classical correlates of protection.

For example, between 12 and 72 months of age only 30 to 50 percent of children have levels above one microgram per mL, and that if one was to compare the antibody data with the clinical vaccine failure data, it would suggest that in the U.K. a concentration of .15 correlates best or better with clinical vaccine failure data.

Why is this? Well, there is certainly evidence that the U.K. vaccine program results in the induction of immunological memory which persists up until at least school age, but clearly there's also good evidence that herd immunity is an important factor in maintaining control of Hib disease in the U.K. and sorting out whether these children with low antibody concentrations at four to five years of age are not getting disease because of their prime; they have immunological memory, or whether they're protected by herd immunity, I think, is a difficult one.

There are other factors to consider though. In fact though we say the antibody levels are low, clearly they're satisfactory through the first

year of life when the disease risk is or at least was highest with 88 percent above one and 99 percent above .15.

David Goldplatt has demonstrated that over the first year after the primary schedule there is avidity maturation, and we've been in a population which has high vaccine coverage.

The catch-up program has probably also been very important in reducing Hib circulation early on in the vaccine program, and this is probably an important point in the success of the program.

I do think that there is a need for further studies in the United Kingdom and, in particular, to look at memory and avidity in older children, preschool, and compare vaccinated with unvaccinated.

Carriage studies, I think, with older children should be done. The last carriage study was in 1996.

I'd also make the point that avidity measures and booster responses are at best surrogates of protection, and the disease surveillance should continue, particularly if combination vaccines incorporating the acellular vaccines are introduced into the United Kingdom.

And I'll just finish by acknowledging the collaborators in these studies, in particular, members of the Oxford vaccine group headed by Professor Richard Moxon.

Thank you.

CHAIRMAN GREENBERG: Thank you.

We now have a moment or two for committee members to catch their breath and ask questions or make a statement if they want.

Dr. Fleming.

DR. FLEMING: Dr. Heath, as I recollect earlier in your presentation, you had given figures for the incidence, and I recollect that you had referred to the pre-vaccine incidence as being 109 per 100,000.

DR. HEATH: Correct.

DR. FLEMING: And in '96, seven, and eight, it was 14, 15 and ten.

DR. HEATH: This is in unvaccinated children.

DR. FLEMING: Okay. So what would it be if you looked at the global population?

DR. HEATH: In all children, regardless of vaccine status --

DR. FLEMING: Exactly.

DR. HEATH: -- it was .8 per 100,000 in 1998.

DR. FLEMING: Okay. Regardless of vaccination status.

DR. HEATH: Correct, yes.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I actually had a question that's very much the same as Dr. Fleming, and I think we're not going to get an opportunity to hear the U.S. data, but the information that was given by Dr. Bisgard's nice paper suggests that the incidence in five to 11 months in the U.S. is 1.16. So, again, it may not be different, but looks a little higher.

However, the data suggests that your rate of disease in the 12 to 23 months is one per 100,000, whereas in the U.S. it's .1 per 100,000.

So I guess one question that I -- it looks like your series of two, three, four or three, four, five works very well, but the question of a booster, it seems that in your older children you have higher rates of disease than were seen. Is that a correct interpretation?

DR. HEATH: I think probably that it is a correct interpretation, although -- and certainly the peak age of Hib disease now in vaccinated children is

the second and third years of life, whereas clearly it used to be in the first year of life.

I think from our perspective it comes down to at what point should we introduce a booster, given that though there clearly is a drop off of vaccine efficacy between the first and subsequent years, it's very small in terms of numbers of cases, and one would have to debate the cost effectiveness of introducing a booster, and I think that's a debate probably for others, but that's what it comes down to, whether, in fact, it's worth vaccinating 700,000 children a year extra to save a relatively few cases.

DR. BISGARD: Could I address the U.S. data? Kris Bisgard, CDC.

In '97-'98, the incidence of zero to five month old of Hib cases was 2.8 per 100,000 and six to 11 months of age was 1.1 per 100,000, and then the one to four year old age was .4 per 100,000.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: Could you elaborate on one of your conclusions that a serum antibody level of 0.5 micrograms per mL correlated best with vaccine failure data, quote, unquote?

So you don't mean --

CHAIRMAN GREENBERG: Point, one, five,