standard and the high of ELISA to see what numbers may correlate to serum bactericidal activity of 1 to 4 or greater?

DR. CARLONE: Well, yes, we've looked at the high avidity and the low avidity ELISA on a small number of sera -- I guess a small number -- using the different complement sources. We have not gotten at that number yet in that correlation because the rabbit complement gives you such high numbers. We don't have a lot of low numbers in those cells. We are tempting to answer some of those questions at this point.

DR. GREENBERG: Dr. Estes.

DR. ESTES: So you just implied that you know that the polysaccharide put on these plates has a different confirmation. Has there been any attempts to try to capture that with, say, monodonol or something to maintain the proper confirmation to measure the appropriate antibody or perhaps more functional antibody?

DR. CARLONE: Well, I think the approach has been to try to optimize the binding on the plate which we know binds both low and high avidity to, I think, correlate it with what we know historically is protective or correlates with protection which is the SBA. So the idea has been to try to modify the ELISA

because it is, if you will, a correlate of a correlate of a correlate so that's been the approach to do. It's a straighter, we think, simpler approach to do that.

DR. GREENBERG: Any other questions?

DR. BREIMAN: Just one quick one. Is there any cross reactivity between the serogroups? It seems to me that I remember a famous CDC immunologist telling me that with meningococcide there may be some cross reactive components.

DR. CARLONE: No. Between the A and the C - if that's what we're going to focus on. The answer is essentially no.

DR. GREENBERG: Okay. Thank you. I would like to move on now to some presentations from some industry representatives. The first person I have talking is Dr. Robert Ryall from Connaught. I would ask that all of you please stick at the worst to the time you are given.

MR. RYALL: What I'd like to talk to you about today is two vaccines that we are currently working on, bivalent AC and tetravalent AC Y & W polysaccharide that conjugated with diphtheria toxoid protein. This is the same diphtheria toxoid protein - -

PARTICIPANT: We're having trouble hearing

you. Is the volume turned up?

MR. RYALL: This is the same diphtheria toxoid protein that we used to formulate BTP. The majority of the talk will address the studies we've done with the bivalent AC and the tetravalent AC Y & W are in Phase I at the moment.

A number of years ago we embarked on a collaboration with WHO and CDC to evaluate in a Phase I study three formulations of a bivalent AC. This study was performed in Niamey, Niger in Africa and is now completed.

One of the things that we wanted to see in this study was whether or not we were eliciting a strong immune response following a primary series. That in itself is good. In this population in Niger the endemic rates are much higher than they are in the United States. They can range from 20 to 30 times higher. They are also subject to group A epidemics that are sicklecal occurring approximately every 10 years.

In nonepidemic years the endemic rate of surogroup C is actually quite high. Again, it approaches 20 per 100,000. During epidemics the epidemics strike not only infants but all of the population. They see a lot of disease in younger

children and teenagers. The WHO is very interested in developing a vaccine that will provide protection not only in the first year of life, which has the highest attack rate, but will provide protection as the child ages.

One of the unknowns is whether or not the conjugate vaccine will provide a longer duration of protection versus the polysaccharide vaccine which is known to not provide long duration of protection in young children.

In this study we had three conjugate groups where both the A and the C polysaccharide formulated at one, four, or 16 micrograms of polysaccharide per dose. We had one group that received the license A/C polysaccharide vaccine and one group that received PRPT, the hemophilus conjugate vaccine as a control.

In this population the hemophilus conjugate is not routinely administered so the other cocmitten vaccines are DTP and OPV.

What we did was vaccinated six weeks, 10, and 14 weeks. We had a prebleed at six weeks of age and post primary bleed at 18 weeks of age. At 11 to 12 months of age we boostered with polysaccharide. This is to really mimic an infection, if you will. It's also to test whether or not we are seeing a

memory response to the primary series. Then we had a one-week post bleed. I'm sorry, a four-week post bleed on the polysaccharide injection.

In this slide or graph we have all the vaccine groups at times zero. I'll show you the actual GMTs. What I'm plotting here is the GMT of the bactericidal activity to serogroup A at six weeks of age, 18 weeks. These two groups here are the PRPT control group and the licensed polysaccharide versus the three conjugate. You can see a sharp rise in bactericidal antibody following the three doses of vaccines.

As the children aged to 11 months of age, you can see that the circulating bactericidal antibody levels declined down to almost approximately the original pretiter level. Upon administration of the polysaccharide vaccine, the polysaccharide group rose slightly but all three conjugate groups rose significantly higher than the polysaccharide group but there really wasn't a significant difference between the three conjugate groups.

This gave us some early indication that we are achieving a good immune response following a primary series but, again, the concern is are these children now susceptible to disease later on or do

they have a memory antibody that will allow them to remain protected. That's with serogroup A. A very similar plat with serogroup C.

The only noted difference is the relatively high maternal antibody to serogroup C which may have attributed to some of the differences in the response following three doses and what we see at 18 months. Again, you see the maternal antibody is dropping off to less than a titer of 10. The three conjugate groups are higher than the polysaccharide. Again, a decline at 11 months of age but a good boost with the polysaccharide to the three conjugate groups and a relatively marginal response with the subjects who had received two doses of polysaccharide.

On this table is the bactericidal antibody responses to both serogroup A and C, the five different vaccine groups, the relative preimmune titer. As you can see, A is down around 10 but the C is up around the 50 to 60 range.

The bactericidal antibody responses following three doses of conjugate versus two doses of polysaccharide were in the 170 to 370 ranges for the three conjugates versus seven for the polysaccharide which is really not any different than the infants who had received no vaccine at all.

Then this group dropped out of the study and at 11 months this is their preimmune titer prior to polysaccharide boost. You can see a sharp rise in bactericidal antibody and about a four-fold rise in the subjects who had previously been vaccinated with polysaccharide.

The same general trend holds true for the group C. Again, the following primary series we have a very good response versus the polysaccharide. They all decay up to 11 and a sharp rise to the polysaccharide boost versus not a very sharp rise in the polysaccharide group.

This study ended at that point and we have a second study that is ongoing. In the second study what we want to do is to evaluate different schedules that may be applicable to this population where we are looking at anywhere from one to four doses in a primary series and then following these children up to two years of age.

As Brad mentioned earlier, we are also looking at the effect of carriage but it's expected in this population given the slow acquisition of carriage we may or may not see an effect but that is one of the things we are looking at.

George just talked about the ELISA antibody.

The bactericidal antibody data that I just showed you was performed by the people in George's lab. The ELISA antibody run by the CDC standardized method, not the high avidity method but the method that measures all the IgG antibody, was performed in our lab in Swiftwater.

One interesting note, and it mirrors what George was saying in his talk, we do see a fair amount of maternal antibody, especially serogroup A. The children have between two and three micrograms of antibody. Group C anywhere from one to two and a half.

Following primary series you don't really note any difference between the antibody levels of the conjugate group versus the polysaccharide group. They are approximately the same. You can see that the maternal antibody has declined to less than one.

Now, at 11 months of age all groups have very little antibody but what we see is a similar trend for what we observed with the bactericidal activity but maybe not as pronounced, anywhere from six to 10 micrograms of antibody per serogroup A for the three conjugate groups versus three for the polysaccharide group and approximately eight micrograms of antibody versus 2.8 for the infants

receiving the polysaccharide.

We are currently following up and looking at the high avidity antibodies that would distinguish if there are any differences using that method in comparison to this data set.

We've run a number of studies throughout the world with the bivalent but we are quite interested in developing the tetravalent, especially given the recent increase in serogroup Y disease. We have performed a Phase I step-down study design starting with adults, toddlers, and then into infants.

This vaccine we formulated three different vaccines, one at one microgram polysaccharide per ml of each serogroup, the second at four, and the third at 10 micrograms per ml. This was essentially a Phase I safety study where we are looking at the safety of the vaccine. It was an open study where we could escalate the dose and look at the safety profile.

This study is completed and we are currently assembling the clinical study report to be submitted to CBER later this year. In the second stage of the study we evaluated two doses of the vaccine in toddlers, very similar to the schedule that was presented in an earlier slide by George where we give a dose of the conjugate at anywhere from 12 to 22

months and then a second dose at two months following that. We have a blood sample prior to the second dose and one month post the second dose.

The third study which is currently ongoing in infants. Again, the same three lots of vaccine. We have a prebleed at two months. One difference is a different schedule that we use. This is a typical U.S. schedule versus EPI schedule or revaccinated at six, 10, and 18 weeks. I'm sorry, two, four, and six months dosing. We have a blood sample at six months and seven months of age.

In this study we're looking at the same sort of polysaccharide boost but at 15 to 18 months of age. In the current study in Niger we have the polysaccharide challenge at two years. We are getting an idea of the duration of the memory antibody by looking at different time points.

There is one paper that has been published recently on the Chiron vaccine and it shows a lot of promise where they followed up after five years. There is a lot of promise that the meningococcal conjugates will be effective.

Lastly, I just want to acknowledge the various people who worked on this project as well as our collaborators. People in these three columns

represent people within PMC who started their collaboration with Bernard Ivanoff at WHL and Kim Mulholland and Jay Wenger, Ann Schachat, George Carlone, and people at CERMES at the site that are doing the study in Niger. Thank you.

DR. GREENBERG: Thank you, Dr. Ryall. We have a few minutes for some questions. Kathy.

DR. ESTES: It's really remarkable when you look at your ELISA titers with the plain polysaccharide in with the conjugates and then you look at your bactericidal titers because there's really quite a disparity in what you get from the polysaccharide and what you get for the conjugate.

I guess the other thing that I wanted to ask is it looks like your bactericidal titer prior to immunization or in children that aren't being immunized with that vaccine has a titer of around six. Again, it's a little hard to know how to -- that's obviously not going to be protected so how that titer extrapolates to a number that we are going to have to try and establish a correlate is kind of interesting. Do you have any ideas what these numbers might be from this?

MR. RYALL: Well, the one thing that we have to do is look at the human complement much like George

described to see if we see the same relative difference. Is there a difference between our vaccine and the Chiron vaccine or the Lederle vaccine.

In all the studies that I've seen so far there is this dramatic decline of antibody and the question is raised is how much circulating antibody -- do you need a certain level of circulating antibody to always be protective. It may be much smaller than we think.

The fact remains that it appears as if we are inducing memory and that was really by design of the vaccine. I think the prevailing mood is that if you do have memory antibody that you are likely to be protective. However, there is somewhat of a leap of faith there I would think.

DR. GREENBERG: Ms. Fisher?

MS. FISHER: In your past and present studies, are the children all adhering to the same vaccination schedule with the other vaccines? Are they being given other vaccines on the same date that they are being given meningococcal? Have you noticed any differences in terms of response?

MR. RYALL: In the majority of our studies the study vaccine was given at the same time as the conjugate vaccines. However, we did have one study,

a very small number of subjects, only 10 per group, where we gave the study vaccine one week prior to the conjugate vaccines. In comparison of those responses, we don't see any significant difference. Again, I shouldn't really say significant because the numbers are so small. There's no noted difference.

MS. FISHER: I'm talking about other vaccines.

MR. RYALL: Yes. This is difficult because we are comparing different populations as well but in this study they have received the fewest number of vaccines. In all of our other studies they have received hepatitis B, hemophilus vaccine as well. This study population was a little unique in that they only received OPD and DTP.

In comparing the responses across those studies, we don't really see a problem with adding on more vaccines to the schedule.

DR. GREENBERG: Dr. Gotschlich.

DR. GOTSCHLICH: In this presentation the issue of memory responses came up. I thought it was very encouraging that, in fact, the response to the polysaccharide following the conjugate vaccines were what appeared to be significantly higher.

Nevertheless, a comment needs to be made

about immunological memory in meningococcal disease. That is that at least in adults, and it's also true in children, although not as much is known, the serum at the time that the patient arrives with meningitis is loaded with antibodies to the meningococcus. The fact that this person is capable of mounting an immune response very early in the disease is not enough to prevent the disease.

That was really the reason for having to do the perspective collection of sera that I illustrated this morning. While I look forward to memory immune responses but to a B cell antigen which it remains. After all, it's not going to see this in the same context of the same T cell epitope. We have to be careful about over interpreting.

DR. GREENBERG: Other questions?

DR. STEPHENS: The question concerns the marked falloff that we see with this conjugate. It relates to the issue of boosting natural immunity. Have you looked at or was there active disease of A and C? I know you are doing a study looking at carriage but was there active disease going on at the time the immunization study was being done?

MR. RYALL: In none of the study subjects did they come down with the disease. Certainly in the

African population I recall study subjects in the same house as siblings who did have the disease but none of the subjects did come down with the disease. Relative to follow-up, I don't believe we've seen any beyond the point of the initial follow-up of the study.

DR. GREENBERG: I'm going to have to stop because we're not -- we're just unfortunately going to have to move on. The next speaker is Dr. John Donnelly from Chiron. Again, since the panel has lots of questions, if the industry representatives can try to be as concise and brief as possible and limit their discussion to slides that have data on them, that might help.

DR. DONNELLY: Thank you. Do we have a pointer? Yes. Good. Okay. I'm going to tell you a bit about the assays that we use at Chiron to measure antibody responses to our meningococcal vaccine, how we do them, and a little bit about why we do them the way we do.

You heard already from Dr. Carlone this morning about the CDC standardized ELISA and the fact that the simpler approach of putting the polysaccharide onto a plate and then just looking at what is bound to it detects antibodies that can be of either relatively high or relatively lower avidity.

The higher avidity antibodies seem to be implicated in functional effectiveness against bacteria and culture. We'll go into that in more detail later.

The end result is in samples that contain mixed populations of antibodies of higher and lower avidity where they contain antibodies of lower avidity to Professor Gotschlich's point earlier, this assay does not correlate well with the bactericidal assay, what we call the BCA for bactericidal assay that others call the SBA for serum bactericidal assay.

Now, with Dan Granoff and George Carlone and others, a modified ELISA was developed that detects primarily antibodies of higher avidity, and as you saw data from Dr. Carlone and you'll see some more data from our group, correlates well with the bactericidal assay.

This slide, similar to the ones Dr. Carlone showed, frames the problem. There's a typo in this slide. This shows the result of the standard ELISA and this should be micrograms per ml, not units per ml. On the bottom axes you see the modified ELISA and this is units per ml and not micrograms.

At any rate, the important take away from this, and this shows a population of three to five-year-olds given either the meningococcal vaccine or

the polysaccharide vaccine.

If you look at the standard ELISA over a relatively narrow range of ELISA titers from about two to about 50 micrograms per ml, you can see a very broad range of bactericidal titers. This is a bactericidal assay that is done with human complement and we'll get into the reasons for that and the specifics of it in a little bit.

Clearly you have a lack of correlation of ELISA titer in the standardized ELISA with the bactericidal assay using human complement. If you look at the pulled data for conjugate and polysaccharide vaccinees, the R value is about .29. I think it's important to consider the pulled data.

If you look at the second panel, you see that what happens in the modified ELIZA where you are now selectively looking for higher avidity antibodies is that relatively speaking some of these values are pulled into line so that you now have an ELISA units per ml range from about .2 up to 100 and a bactericidal titer range of from eight up to several thousand.

The other point that I wanted to make is that there is a continuity of response here. The pulled data gives a correlation coefficient of .87.

If you look at the population of higher avidity antibodies from polysaccharide antibodies on up to conjugate, you see a difference in magnitude. What you don't see is a lack of continuity between the two vaccines.

I think it's important, as Dr. Carlone pointed out earlier, you have an assay that is dependent on antibody activity but independent of vaccine.

So the way that we arrived at this, and this as I mentioned, is work of Dan Granoff and George Carlone and others, was to make two modifications. One is our assay uses derivatized polysaccharide coated onto the ELISA plate. Dan and others did a number of studies to show that the specificity of this test is very high using competitive inhibition and to show that the polysaccharide coated on the plate is antigenically equivalent to the native polysaccharide purified from the bacteria. Obviously a very important point because if you use a modified antigen, you need to know that you are detecting with high fidelity antibodies that recognize the native antigen.

The advantage of this approach is that it gives you a very solid coating of antigen onto the ELISA plate. That allows you to perform the next step

which is the incorporation of a chaotrope salt, in our case ammonium thiocyanate to minimize the binding of the low avidity antibodies.

We selected a concentration of about 75 millimolar to give us the maximal discrimination between a sera that had bactericidal activity and sera that didn't. The resulting assay gives quite a good correlation with the bactericidal assay. I'll show data to explain this choice in just a second.

If we can go on to the next one, this is one of a variety of experiments that we did to show the antigenic equivalents of the antigen that is on the ELISA plate in our test. Here you see a selection of sera from polysaccharide vaccinees. These are adult sera but we have also looked at infants and young children.

We've titrated in native polysaccharide in increasing concentrations. You can see that in all cases with a sufficiently high concentration of native polysaccharide we were able to basically abolish the signal in the assay. Using various other controls we can show that the antibodies that we are detecting are specific for native polysaccharide. That's one important issue.

The second important issue is how much

chaotrope to use. Here you see a comparison of an adult serum and two toddlers, one toddler which has bactericidal antibody and one toddler which doesn't, although both of these individuals were positive by the standardized ELISA.

What you see is as you increase the thiocyanate concentration, toddler two who lacks bactericidal antibodies falls out at much lower concentrations of thiocyanate than does either the adult or toddler one who does have bactericidal activity and a concentration of about 75 millimolar which is approximately here on the curve. You can see we get quite good separation in binding between BCA- and BCA+ samples.

Now, this slide was shown to you by Dr. Carlone a little earlier but I'll go through the key points again. This was a set of about 30 three to five-year-olds that were looked at with a bactericidal assay using human complement. There is a typo on Dr. Carlone's slide, as he mentioned. This is the corrected data here. You can see that post dose one the conjugate vaccine is giving a cidal titer of about 74 and the polysaccharide of about 14. You go out to post dose two and you see there is a bigger disparity here, a ratio of about five-fold and a bit more than

20-fold.

If you look at the standardized ELISA you see that you can't distinguish between the two vaccines either post dose one or post dose two. If you look at the modified ELISA with its preferential ability to detect high avidity antibodies, you see about a five-fold difference post-dose one and about a 20-some-fold difference post-dose two just as you see in the bactericidal assay.

So we believe that this method gives us a way to detect antibodies that are of higher avidity and that are more likely to be functional.

Now, let me turn to a discussion of the bactericidal assay that was described nicely by Professor Gotschlich this morning. A number of methods are in use in literature, the one that was originally published by Goldschneider, Gotschlich, and Artenstein; a method that is used at the Center for Disease Control and the Public Health Laboratory Service that was published by Maslanka which uses rabbit complement; Chiron bactericidal assay which was based on Goldschneider's method with some modifications and it uses human complement. I'll show data to show that our assay correlates well with the method of Goldschneider, et al.

Just for techies in the group, a comparison of what the differences are. Both Goldschneider and the CDC PHOS group subcultured their bacteria on solid media. We made a decision to use a subculture in broth. This adaptation allows us to get a somewhat higher frupote in our assay makes it more readily applicable to larger numbers of samples.

We and Professor Goldschneider's group used human complement where the other groups tend to use rabbit. The assays that have been done more recently tend to use a 60 minute incubation in the presence of C02 and that's true for the CEC assay and for ours.

In our hands, at least in the Chiron assay, the bacteria grows during the 60-minute incubation so that in the presence of complements and media and no antibodies for a serum that has no cidal activity, we'll see approximately a doubling in colony counts over the 60-minute incubation period.

Now, I would like to have an opportunity to discuss this with Professor Gotschlich not having seen his original colony counts. At least in our hands when we reproduced this method from the paper, we didn't tend to see growth during the assay. Dr. Carlone and his colleagues report that also there is not growth in the 60 minutes using this method.

That makes this a somewhat more stringent method because of the way the numbers work out of doing the colony counts at the zero time and again at 60 minutes. To kill half the bacteria here, you only have to remove half the starting inoculum where here you have to remove an amount that is equal to the starting in inoculum.

This shows a comparison of a set of about 80 samples from three to five-year-olds that were assayed in our laboratory by the two methods, the method of Goldschneider, et al., or the method that we have had validated for use in our clinical program.

You can see that for both conjugate and polysaccharide vaccinees shown in the two different colors, there is quite a good straight line fit. The correlation troefficien of the pulled data is .88 so that we can establish a pretty good relationship between the two methods.

Particularly there's not a lot of evidence that the distribution is being pulled one way or the other where, if you recall, the comparison of rabbit and human complement that Dr. Carlone showed, the two regression lines clearly diverged as you went to higher titers for different data.

So if you look at some live data, and this

is a group of about 80 three to five-year olds, and compare the method that we are using to measure cidal antibodies with the method that was published originally by Goldschneider, Gotschlich, and Artenstein, in this particular group in the conjugate vaccinees post one we had quite similar geometric mean titers between the two methods for both the conjugate and the polysaccharide vaccinees.

Using a cutoff of one to four as the threshold for a positive sample, which was what was used in Professor Goldschneider's paper, we found basically identical results as far as the percent greater than four among the conjugate vaccinees and likewise among the polysaccharide vaccinees.

At Chiron we've chosen to use a cutoff of one to eight in the human complement assay. That gives us, we feel, an extra measure of stringency of not miscalling a false positive sample. You can see that slightly affects our percent sera conversion relative to Goldschneider's original numbers. But actually there is still quite a bit of overlap between the confidence limits. The same relationship holds true for the polysaccharide vaccinees.

Now, you've seen some rabbit complement data all ready. We have also looked at rabbit complement

on the same dataset. I won't go into a lot of details other than to confirm Dr. Carlone's observation that the use of rabbit complement tends to yield much higher results both in conjugate vaccinees and in polysaccharide vaccinees. It's not absolutely clear what the relationship between titers determined by these two methods really is.

Now I would like to show you a little bit of clinical data to make a couple of points. This is a study in 15 to 23-month-olds who received two doses of conjugate followed by a dose of polysaccharide. Here you see in the white bars the conjugate vaccine. In the black bars polysaccharide vaccine given at the same times. In the gray bars an unvaccinated placebo control.

These are bactericidal antibody titers that we get a response geometric mean about 10 after one dose in 15 to 23-month-olds. A second dose of conjugate gives us still a higher response whereas there's only a very limited response to the polysaccharide vaccine and no evidence of boosting.

We came back at 12 months later and looked at the titers and you can see that although there is some decay from the feet, they are still above baseline and the mean is still above 10.

When we boosted all three of these groups with polysaccharide vaccine, the toddlers that were primed with conjugate showed a very substantial rise. The toddlers that were primed with polysaccharide basically did not respond at all. The key take-away from this is that in this age group the conjugate vaccine primes well for a response to the polysaccharide and elicits a good response post-dose one. The polysaccharide response does neither of those things and, in fact, may prejudice if it's given too early the ability to respond to the later dose of polysaccharide vaccine.

In the next slide you can just sort of get the gestalt of this is the modified ELISA titer showing the higher avidity IgG antibodies. The pattern of the bars is much the same.

You do see a little bit more ELISA response with the polysaccharide vaccine whereas the bactericidals were very low. Again, there is no evidence of memory whereas there is substantial evidence of memory in the conjugate vaccinees.

And I would like to close with some infant data if I could have the next slide, please. These are bactericidal responses of U.K. infants given the three doses of conjugate at two, three, and four

months of age at zero, one, and two study months.

We weren't able to assay all of the presamples by bactericidal because the samples were not very large and the assay consumes a lot of specimen. We looked at a subset of about 16 infants and we found that they were less than one to four, an interesting difference from the Los Angeles study in 1944 that Professor Gotschlich talked about. This is 40 years and halfway around the world and I'm not sure what the relationship is.

At any rate, we didn't find bactericidal antibody in two-month-olds but we certainly did find it after one dose and also after two doses of conjugate and again in this population when we waited eight months and came back with a boost of polysaccharide.

This is 10 months of age so these children would not normally be able to respond to the polysaccharide vaccine. And you see that here in the control group which didn't receive conjugate but did receive polysaccharide and basically failed to respond at the age of 12 months. We get a nice memory response in the 12-month-old kids that were primed with conjugate at two, three, and four months. This looks much like the response to the Hib vaccine.

To close, the data that you've already heard about from Professor Gotschlich using the Goldschneider BCA provides a very useful bridge to protection from disease in young adults. When we compare the bactericidal assay that we use at Chiron which uses human complement to the results obtained by the Goldschneider method, we get very comparable data.

The modified ELISA is a very useful test. It detects higher avidity IgG antibodies and it's much easier to do than the BCA and in our hands by this method correlates quite well with the BCA.

Lastly, as far as the vaccine, we found it to be immunogenic in all the populations we've studied including infants. We found it to elicit protective levels of antibody by bactericidal methods in infants, toddlers, and adults and to demonstrate both initial response and priming for memory response to the polysaccharide.

From these data and using these methods, we think that it is possible to make a determination of efficacy based on measurement of serological endpoints.

DR. GREENBERG: Thank you, Dr. Donnelly, for giving us a lot of information quickly and concisely. We have a moment or two for a few questions.

Can I ask a question? This is a very naive question. I don't know this field so I'm now thinking all the data of the correlation of serology with protection is based on a natural history study sort of from Fort Dix.

Can somebody bring me up to date on what the correlation of serology to protection was in the polysaccharide vaccine studies? What did we learn from those studies that registered those polysaccharide vaccines that gives us a number or a place to aim for?

DR. GOTSCHLICH: I'm afraid you're looking at me.

DR. GREENBERG: You were the person who talked about serologic correlates of protection.

DR. GOTSCHLICH: Ultimately the question is a very difficult one. In the time period where trials were done for efficacy and serological tests were done, they were all by the radioimmuno assay either done in my laboratory or done in Finland in a comparative assay.

If you do the correlation that you wish to do, mainly to look at the immune response and correlate it with the efficacy data you come up with the feeling that probably one to two micrograms of

antibody four weeks following immunization is protective for a period of a year.

DR. GREENBERG: Okay.

DR. GOTSCHLICH: I would, however, caution you that is primarily group A data and not group C data.

DR. GREENBERG: Right. And you cautioned me that it was a notion, not a fact.

DR. DONNELLY: Also, without a study to bridge the RIA to the cidal, it's really hard to know what the connection is to the modern assays because the RIA data hasn't been generated.

DR. GREENBERG: Ms. Fisher.

MS. FISHER: So, Dr. Donnelly, with these studies you are predicting a year's worth of immunity or how long does immunity exist?

DR. DONNELLY: From meninge C per se it's difficult to make that conclusion. The studies of Hib, which I think are the next nearest parallel where it's possible to elicit antibodies with a conjugate vaccination regimen in young infants and elicit a memory response at 12 months through a booster of polysaccharide, once those children have received a course of immunization at two, four, and six months or on the European schedule and a booster, protection

seems to be quite long lived.

MS. FISHER: But because this disease is in older populations also, are we looking at a situation where there will be boosters throughout life?

DR. DONNELLY: I think that remains to be determined. I think one would have to do the studies. I believe that the U.K. is intending to basically vaccinate a very large age range, up to age 18, in their vaccination campaign.

So there may not be an opportunity to collect data there on what the responses are going to do over time. I think the question of memory versus antibody titer is an important one. Professor Gotschlich raised the view that since people with active meningitis can have quite high titers of antibody if you need antibody for prophylaxis.

For example, in invasive meningococcal disease, vaccines that are very efficacious at the time of boosting at 12 months rarely have any -- well, at least a third of the kids frequently are sera negative by quite sensitive assay.

A couple of possible take-aways from that, the amount of antibody that is required for protection may be quite small. Or that the memory may be just as important or more important than the mass amount of

antibody in the circulation at any given time. I think that has to be determined by further tests.

DR. GREENBERG: Last question. Dixie.

DR. SNIDER: Well, with regard to the comment about the titers and the earlier comment about people, if I understood correctly, who have meningococcemia having terminal complement deficiencies, I'm wondering what I should take away as a message about those high titers. I mean, are the high titers not protective in those individuals or are they just not functional antibodies because they don't have the complement that's necessary to complete the bactericidal activity?

DR. DONNELLY: That's a good question. Address that to Professor Gotschlich as to whether in sera from people with acute meningococcemia there was every an opportunity to look at functional activity. You would assume that since the live bacteria are there, that they are not getting killed by the antibody complement but you would have to do an experiment.

DR. GOTSCHLICH: I think I would like to limit, because I don't want to obfuscate anything, it's simply to the fact that RIA antibodies are present in very high titers as are hemagglutinating

antibodies.

The only other thing that can be said is that the convalescing serum two to three to four weeks later is clearly highly bactericidal. Of course, the majority of these individuals do not have genetic complement defects. Whether you are addressing yourself to whether they are decomplemented during a meningococcal infection I cannot speak to, but there may be infectious disease experts who can.

DR. GREENBERG: I know that we could go on with this but we have another industry representative and I really do not want to get behind schedule here. I'm going to call this one and we can come back and touch on this in panel discussion if people feel it's necessary.

Our final presentation from industry is from Dr. Peter Fusco from the North American Vaccine.

DR. FUSCO: I'll be speaking about serologic studies on group C meningococcal conjugate vaccines. This will be focused mostly on showing a lot of correlations between bactericidal activity and the IgG measured by ELISA. Before I get into those correlations, I'm going to also talk about the nature of the polysaccharide of this conjugate and how it differs from most of the others you've heard about.

This is group C conjugate where we're using a De-O acetylated polysaccharide. It's 10 microgram polysaccharide dose, 15 to 20 micrograms tenus toxoid conjugated by reductive emanation and it's absorbed with aluminum hydroxide.

The key here is that we're using a De-O acetylated polysaccharide. What that means is that there is an acetyl group here on the oxygens of the C-7 and C-8 for this polysaccharide and this acetyl group shifts around. It's not constant. It can be in either position but not both. Also it may not be there at all. You can have variations in percentage of O acetylation.

What we've chosen to do is remove this all together for our vaccine so it's a De-O acetylated polysaccharide. This may also have an impact on how you do your ELISAs and how you measure your antibodies.

The rationale behind this deal of O acetylation, basically it's already been shown that the De-O acetylated polysaccharide elicit similar or better responses in humans when compared with the O-acetylated. Preclinical studies have also shown this. Recent clinical studies have shown greater immunogenicity with this De-O acetylated

polysaccharide.

The De-O acetylation eliminated inconsistency in the manufacturing of this product so you don't have to worry about where the acetyl group is appearing if it's appearing there at all.

Also, the last point here, I think, is really critical. We've got some competitive inhibition data now that is confirmed that it looks as though bactericidal antibodies are directed against De-O acetylated epitopes on O acetylated bacteria.

Here is an example, some evidence to support this. This is looking at some mouse sera raised against the conjugate vaccine. This is a competitive inhibition bactericidal assay. This id distinctly different from a competitive inhibition ELISA. We're looking at blocking the actual killing antibodies that are directed against the bacteria. We are using the O acetylated bacteria.

As you can see here with these two different sera, we're getting the same kind of inhabitation using this De-O acetylated polysaccharide. This is the purified polysaccharide. When you use the O acetylated polysaccharide in the same quantity, you are getting much less inhibition. You're looking at orders of magnitude differences here in the

effectiveness of this inhibition on the sera. This is basically telling us that these antibodies are really focused on the De-O acetylated epitopes or the bug.

We've seen similar results in humans. This is just one example from some infant data, an infant receiving the primary immunization. Again, the De-O acetylated polysaccharide is inhibiting much better than the O acetylated polysaccharide even though we are using an O acetylated bacteria in this assay.

And this is just to show again that De-O acetylation is not detrimental in any way for this vaccine. This is a slider bar from Peter Richmond. The PHLS presented this at the Neisseria conference last year. It shows bactericidal activity with sera conversion and IgG and, again, sera conversion. This was also using everything O acetylated.

As you can see here the De-O acetylated conjugate compares quite favorably with the other vaccines. There's no problem using the De-O acetylated conjugate here.

This is our clinical development plan in the U.K. that's been going on now for the last two or three years. We are obviously in different phases of these studies in different target populations. The point I want to make here is that I'll be showing you

data really from the top three studies; adults, infants, and toddlers. I just showed you some toddler data in the previous slide. That previous slide was after a single injection in toddlers that had never been vaccinated before.

Typically this is what you see in terms of the kinetics of the response. In infants receiving a vaccine at two, three, and four months of age, you get a nice rise in IgG. Also bactericidal rise that parallels the IgG showing this clear correlation. The IgM, on the other hand, levels off. This is something we have investigated further. It's clear that the IgG is what is correlated. The IgM is not.

Now, the point I want to make here is we are using rabbit complement in our assays. Here is where we have prepared the rabbit complement with the human complement. This is using infant sera after one, two, and three injections comparing the bactericidal titers with rabbit complement versus bactericidal titers with the human complement. You can see here a fairly right correlation between the two.

However, it has been pointed out before there is a different, a clear difference, in the titers that you generate. You generally get higher titers with the bactericidal -- I mean, you get higher

bactericidal titers with the rabbit complement.

So you can look at this in terms of the ratio of the titers. If you take the ratio of the rabbit to the human titer and then plot the distribution of those ratios, this is what you see.

Essentially most of the ratios are falling down around 5 or less and the average ratio is 4.4 which is similar to what others have reported. Basically what we're saying here is that the rabbit titer is going to be about 4.4 fold higher than the human complement titer.

Now, getting back to the correlations, this is looking at the IgG correlation with bactericidal titer. In this case we're looking at the conjugated polysaccharide vaccine versus the unconjugated licensed vaccine in the U.K. in adults.

Again, this shows good correlation regardless of what you're looking at, although the conjugate is coming out at a higher titer than the unconjugated polysaccharide.

Now, I just showed you what was correlated. This is what's not correlated. In adults the IgM titer is clearly not correlated with the bactericidal titer. This is the same adult sera that you just saw

previously.

Also, when you look at the infants there may be some small correlation but it's really very poorly correlated. This is after receiving three injections in the infants. The IgM is clearly not really correlated to bactericidal activity.

Coming back to the IgG, this next series of three slides are going to show you the immune response in the infants after each injection compared to the adult data. The adult activity here is represented by the yellow diamonds and the infant data are these blue stars. Again, we're looking at IgG versus bactericidal titers.

What you see here is that both sets of data correlate very well but the infant data seems to be shifted a little bit away from the adult data which would indicate that you're getting less bactericidal activity per microgram of antibody after one injection. Remember, these are infants that receive one injection at the age of two months. This is the response at three months of age.

However, when you get to the second injection at four months of age, the infant data is essentially superimposable on the adult data. They are showing basically the same kind of correlation

between the IgG and the bactericidal activity. By the third injection, again they are essentially the same as the adults.

This slide is just to basically put everything all together in one slide where we have infants, adults, pre and post, conjugated, unconjugated. Again, we just generally see very good correlation between the IgG and the bactericidal activity.

Again, I want to point out that the IgG ELISAs that we're running are using the De-O acetylated polysaccharide as a coantigen.

In conclusion, strong correlations were observed between the rabbit and human complement for the SBA in infant sera at three to five months. Also between the IgG and SBA in both adult and infant sera with rabbit complement.

The rabbit complement provided greater SBA sensitivity compared with human complement. IgM was purely correlated with the SBA. The infant SBA versus IgG correlations after two and three injections were essentially identical to the adult correlation. Thank you.

DR. GREENBERG: Thank you, Dr. Fusco. Can we get the lights? We have some time for some

questions if there are any. People are getting into serologic overload I bet.

I'll start off. It looked to me like I had just been set up to feel that the high avidity ELISA was the way to go. Your ELISAs are not high avidity. Correct?

DR. FUSCO: That's correct.

DR. GREENBERG: But your correlation looked quite good.

DR. FUSCO: Let me qualify that a little bit. Whether or not it's high avidity, I can't say for sure on a relative scale but I can say that we did try to investigate this a little bit using Dan Granoff's technique. In fact, we're still doing some studies on this. We're trying to work out a high avidity ELISA in our laboratory. When we added the thiocyanate to our ELISA, it essentially had no effect. The net effect is that we may be actually looking at higher avidity antibodies when using the De-O acetylated polysaccharide.

DR. GREENBERG: Okay. That would be a good understanding of it. Kathy.

DR. ESTES: I had a question where you compared this serology of your vaccine and the Chiron and the Y. I was left a little bit confused about

that. Were you comparing all of those post vaccinations sera using the De acetylated method as your ELISA?

DR. FUSCO: Actually that was not our data. That was data generated in Ray Borrows' laboratory and was presented by Peter Richmond. At their lab they use the O acetylated polysaccharide in the ELISA. They also use the O acetylated bacteria in the SBA. I should point out, too, that all of our SBA results are with the O acetylated bacteria.

DR. ESTES: Okay. So in that assay that you showed us then, the coating ELISA was O acetylated.

DR. FUSCO: That's right.

DR. ESTES: Okay.

DR. GREENBERG: Do we have other questions here from the panel? If not, thank you very much. We will move on then to Carl Frasch who is going to put all of this back together again I hope.

DR. FRASCH: Okay. As it turns out, I think my talk is basically going to be a summarizing of everything we have heard. It wasn't initially designed that way but here goes.

Again, we are looking at the use of immune surrogates for demonstration and protective efficacy of meningococcal vaccines.

To sort of reiterate a little bit, the critical role of bactericidal provides the immunity to meningococcal disease. We saw that the highest incidence of meningococcal disease occurs in infants between six and 12 months of age at the point when they have the lowest levels of bactericidal antibodies.

Two, studies by Goldschneider, et al., in U.S. Army recruits showed a direct correlation between susceptibility to meningococcal disease and absence of serum bactericidal antibodies. That is, the large portion of individuals for which there were bactericidal antibodies, there was zero cases of meningococcal disease in that recruit population.

Now, we've heard a number of times today individuals deficient in complement component C5, C6, C7, or C8 have markedly increased susceptibility to systemic meningococcal disease. However, I would like to point out that almost no one died in this group. Therefore, it's not just bactericidal antibodies. It's just that it's efficient if you don't have bactericidal antibodies. Probably ultimately phagocytosis ends up clearing the infection.

By contrast, there's a group of individuals unfortunate enough to be deficient in proparatin, part

of the ultimate complement pathway. There is a very high mortality rate among these individuals.

Just to point out to you again that there are a number of manufacturers working on meningococcal vaccines. I'm telling you what has been publicly reported. Chiron corporation is working on A and C. North American Vaccine on C. Pasteur Merieux Connaught on ACYW135.

You can see these are actually rather different vaccines because the carrier proteins are different, conjugation technologies are different. The same story that we've been looking at for hemophilus and meningococcus. We're going to end up with a number of different vaccines.

Now, I want to reiterate using a meningococcal group C polysaccharide study when the vaccine was used in British Columbia on children in which they immunized essentially all the children between two years and 19 years of age.

Now, what we see on the first part is the ELISA looking at percent of individuals with greater than two micrograms per ml. We can see that in the three age groups two to six, nine to 12, and 13 to 19 years of age there is essentially no difference between these three groups.

Yet, when we look at the bactericidal again, percent of individuals with a titer greater than one to four. I think the sera conversion rates are probably more important to look at than just the geometric mean titers.

Now, here we see quite a difference in the age groups looking at bactericidal antibody with the teenage group obviously having the best sera conversion rate. Therefore, the standard ELISA without chaotropic agents simply did not correlate with the bactericidal results.

Now, I would like to bring up another topic that was only mentioned sort of tangentially but I think there's another factor that should have some consideration today and that is a recently reported problem of group C polysaccharide vaccine. This is the observation of a persistent hyporesponsiveness state following immunization of adults, toddlers, and infants.

The hyporesponsiveness was demonstrated by reimmunization of persons who had previously received the group C meningococcal polysaccharide vaccine with the polysaccharide. Their responses were much lower than those of age matched controls receiving the polysaccharide vaccine for the first time. I would

like to illustrate these points in a few slides.

Again, now we're looking at adults. This is a study that was reported by Dr. Granoff, et al., in 1996. What we see is, again, this is a meningococcal priming vaccine, individuals who received no vaccine, had received the standard polysaccharide vaccine, or the conjugate vaccine. Now, the interval between receiving the vaccines and receiving a one microgram challenge dose was four years.

What we see is individuals who received as one microgram of polysaccharide that had no previous vaccination had a really very reasonable bactericidal titer. There was a markedly less antibody response if they had received the polysaccharide before.

Now, if they had received the conjugate before as we have heard today, the conjugate vaccinated individuals are primed and so there is a large increase from the preimmunization level to 28 days post-immunization.

Now, we are going to looking at toddlers. First we are going to look at the ELISA and then we'll look at the bactericidal. What we have here is primary immunization and then finally 12 months past the second immunization, and then the polysaccharide booster.

What we see here looking at the polysaccharide first is that the levels in those who received the polysaccharide before are actually lower after the polysaccharide booster than in individuals who had received hepatitis B control vaccine and finally at the end received the booster.

Again, what we see with the conjugate, the antibody persistence after 12 months is reasonable. However, the polysaccharide boosted the ELISA response very nicely.

Now, looking at the same groups of individuals but now looking at the bactericidal, what we see is, one, again the higher bactericidal titer than those who received the polysaccharide for the first time.

Again, we're looking at percent of individuals with a titer of greater than one to four. There was essentially no change on reimmunization with a polysaccharide. On the conjugate we see two things. One, twelve months after immunization with a conjugate we still have over 85 percent of the children with measurable bactericidal titers and that increased to 100 percent after the polysaccharide booster.

Again, in toddlers we see some difference in polysaccharide boosting when the toddler had seen the

polysaccharide before.

Now, I would like to move to the next slide, please, and we're going to look at the infant. Now we are going to go to Gambian infants. There are Gambian children at 20 months of age at the time of reimmunization who had received a meningococcal vaccine as an infant.

This column lists the initial vaccine, again the initial vaccine being given as an infant, and then the reimmunization vaccine. What we see is if there is no vaccine before, they receive the polysaccharide. They get a nice ELISA antibody response as a toddler. The bactericidal response is respectable.

If they had received two doses of the polysaccharide vaccine and they are reimmunized with the polysaccharide, we see a much lower and negligible bactericidal level. Now, of these individuals who had received the polysaccharide received the conjugate, the conjugate was able to overcome whatever effect of having received the polysaccharide before and we get a good ELISA antibody level and they didn't do bactericidal in these children.

Now, had the initial vaccine been two doses of conjugate, receiving either the polysaccharide or the conjugate, they had a very robust booster response

and a bactericidal titer of over 4,000.

What we would like to look at is this number versus this number. There's a remarkable difference between having received two doses of polysaccharide versus two doses of conjugate and then reimmunization with the polysaccharide.

So, to conclude, and you'll see these questions later again, the questions the FDA would like to ask the committee is; (1) can we use immunological correlates to demonstrate protective efficacy of meningococcal conjugate vaccines. First, for individuals for which the current polysaccharide vaccine is licensed. That means for individuals aged two years and above.

Then, (2) for infants and toddlers below two years of age. Then, two, for both age groups can the presence of bactericidal antibodies be used as a measure of functional and, therefore, presumed protective activity.

Then, (3) can total antibody quantitated by ELISA in some fashion be used as a surrogate for functional bactericidal antibody and, therefore, protection. These are the questions we would like the committee to consider. Are there any questions?

DR. GREENBERG: Thank you, Carl. I think

your questions, there aren't a lot of them. They may take a little while to go through. We are going to be breaking for lunch. I think this is an opportunity if you have any critical questions of Carl that he can answer. We have the open public hearing but this is your last crack at Carl before we get back to this. Does anybody have any?

DR. FAGGETT: I just want a clarification, Carl. Second question says both age groups presence of antibodies used as the measure of functional activity. Don't you mean as a measure? You're not saying that you want that to be the only measure.

DR. FRASCH: You are correct. It's a measure.

DR. FAGGETT: Thank you.

DR. GREENBERG: Dixie.

DR. SNIDER: You can tell me -- you will tell me if this is not appropriate now. The point was made about passive immunity with regard to one-month olds. That is all I heard this morning about passive immunization. I wondered if there is any more information that hasn't been put out on the table for us to consider.

DR. GREENBERG: If somebody can answer that briefly.

DR. FRASCH: There's very little information on the use of passive immunizations. There is some data that Dr. Gotschlich may remember from Dr. -- anyway, a Czech investigator using hyperimmune serum as a way of protecting against meningococcal disease in sort of a day care setting in Mongolia, was it? And they demonstrated some effectiveness of passively administered antibody.

DR. GOTSCHLICH: I think the more telling thing is that children with A gammaglobulin anemia are protected against meningococcal infection by the standard immunoglobulin treatment.

DR. FRASCH: Good point.

DR. GREENBERG: Other questions?

DR. FRASCH: Dr. Bud Anthony.

DR. ANTHONY: Bud Anthony with the Biologics Consultant Group. Carl, in the studies of bactericidal polysaccharide immunoglobulin, was there enough meningococcal disease in those populations to make any conclusions about protection?

DR. FRASCH: I have heard no data whatsoever on that point. The bactericidal polysaccharide immunoglobulin did contain antibodies against the four meningococcal types. The only data that was reported was against hemophilus and then against pneumococcus.

DR. GREENBERG: I'm going to ask one question just to get back to this issue of whether it is absolutely not possible to do an efficacy trial just so I'm clear on that. That is, that there is no possibility anywhere in the world with reasonable resources to carry out an efficacy trial in any population with either for meningococcus A or C? Is that correct?

DR. FRASCH: I would like Dr. Perkins to address that. However, from the standpoint of the FDA, we have to look at not only whether it's possible but whether the epidemiology and other conditions in that foreign country are translatable to the U.S. population because ultimately that's the population we want to protect.

DR. GREENBERG: I totally agree with that. I just, again, for my own thinking about this since surrogate markers are always very important and if we have them, they make things much more efficient. You do like to think of them in the context of whether if it is impossible to do efficacy, then you have to figure out some other way to judge your vaccine. If it's possible, then there's an alternative and I just want to know.

DR. FRASCH: Dr. Perkins, please address

that.

DR. PERKINS: It's possible to do efficacy trials in other parts of the world, I think, for both C and A. It's not possible for the W135 or the Ys. I think the major barriers are the places that have high enough rates of disease to do it efficiently have relatively poor infrastructure.

The other major barrier is the ethical barrier that Emil alluded to with a vaccine that is licensed, at least in the United States, for two years and above and in many places is used in populations younger than that.

Africa, for instance, where we used the currently licensed polysaccharide down to six months in writing. Actually we use it down further than there. I mean, that ethical consideration has been considered by most to be an absolutely contra indication to doing a placebo controlled trial.

DR. GREENBERG: I meant a polysaccharide control trial in very young children where you expect the polysaccharide to be not very efficient.

DR. PERKINS: The sample size limitations would, I think, be prohibitive in those situations.

DR. SNIDER: There's also another ethical issue that needs to be brought out. That is, as you

know, there's been a lot of discussion and criticism around the perinatal pretrials and subsequently other trials. There is the issue if you try to do it in another part of the world what are you going to do about making vaccine available to those people?

DR. GREENBERG: Diane.

DR. GRIFFIN: This is again just to sort of solidify my thinking as we try to tackle this issue and to understand that there is absolutely no animal model available for asking some of these questions including chimps, baby rhesus macaques. No animal like that is susceptible to this disease and, therefore, we can't ask these kinds of questions in a relevant primate trial.

DR. FRASCH: That's true. There is no viable animal model. The meningococcus is uniquely a disease of man and we don't understand exactly why but it probably has to do with the fact that the bacteria must establish itself through attachment to meningococcal tissue and the receptors that uses probably are lacking in some of the nonhuman primates.

DR. GREENBERG: Dr. Daum.

DR. DAUM: I want to press a little bit about these ethical issues because I think to toss out the option of doing an efficacy trial without every

stone looked under would be a shame. I guess that is to wonder whether it's routine in some of these foreign countries. I don't know which ones you're speaking of. Is it routine to immunize young children with the plain polysaccharide vaccine there or is it, in fact, an idea? The vaccine isn't really available there.

I raise this issue because I was impressed in the hemophilus story in Chile PrPT was licensed there but unavailable. There was already epidemiologic data in that country to say flu is a problem. There was already antibody data with that vaccine in Chile in children to say that they responded.

Yet, because the vaccine was unavailable to Chile in children despite licensure in that country, a trial went forward. That trial was half the kids in Santiago got vaccine and half didn't and they compared the occurrence of invasive hemophilus disease. This was fairly recent, way after we know lots and lots about H flu disease.

If, in fact, the vaccine is unavailable for young children in that country, and most of us in this country feel like it's not of great value in kids under two years of age, then is that a real ethical

concern that some people us it as six months or could we find the place to do it where infants could be immunized with a conjugate and controlled with placebo?

DR. FERRIERI: Could I add to the question? Why could it not have been done in England in the U.K. where the vaccine will now be used widely?

DR. DAUM: You can but I would still like my question addressed.

DR. GREENBERG: Dixie.

DR. SNIDER: It's like taking a two-day meeting that we've had around these issues and trying to summarize it. All I was trying to say is that is a problem to address. How would you make the vaccine available? What efforts will you make as a sponsor of these kinds of trials? It doesn't mean that you have to buy it yourself. All I'm trying to say is this is one of the problems you have to deal with. You have to think through before you organize such a trial. It's probably best to just leave it like that.

DR. GREENBERG: Hold on one second. I have a feeling for this question. I think we all do. I didn't mean to solve the question of carrying out vaccine studies in less developed countries here. I just wanted to know this discussion started with an

assumption, a clear-cut statement that this couldn't be done.

If I read this correct, that isn't exactly correct. It could be done. There are mitigating questions, ethical questions, and population questions that would leave you to say, (1) it's going to be hard to do, and (2) the results might not be directly transferable to the United States. Is that a good summary?

Do I have any other questions? Diane.

DR. GRIFFIN: Just one small one that relates to this. It looked to me like the polysaccharide vaccine might actually be detrimental to give it to very young infants. I guess I'm a little puzzled by why this is considered such a good thing to do.

DR. GOTSCHLICH: May I answer? It's a long-established fact that the group C vaccine causes an immunological tolerance which was reported to you today in young children. This effect, at least in our studies, disappeared by the age of two years. In other words, once you immunize children at the age of two years, you no longer saw this immunological effect.

Let me just say one additional thing. The

way it was elicited in these particular studies was by immunization with a microgram of group C polysaccharide which is nowhere near anything like a dose that one would normally consider. That's all I wish to say.

DR. GRIFFIN: But the primary immunization had still been given to very young infants and it's just --

DR. GOTSCHLICH: The recommendations of this country and the WHO is that the group C vaccine not be given to children below the age of two. The recommendations only apply to the group A vaccine where a completely different immune response is seen; namely, a booster response if the vaccine is given at age three months and followed at seven months.

DR. DAUM: What about Dr. Perkin's comments then that it's frequently used at six months of age?

DR. PERKINS: Yes. I do not know how to reconcile the invitro immunology that Carl presented with 20 years of observational experience with this vaccine. There is essentially no clinical information that would suggest that persons at whatever age when given a single or multiple doses of the polysaccharide vaccine are at subsequently increased risk for invasive disease. Although we haven't tried to

address that question head on, there is lots of anecdotal experience that would suggest if there is an increased risk, it must be very small.

DR. GREENBERG: Do I have --

DR. GOTSCHLICH: May I make one last comment? In your question, and it is an appropriate one, to persist to try to see if there is a possibility with efficacy studies, I would also tell you that the only conceivable way to do this is under conditions which are no longer considered ethical, at least by the New England Journal of Medicine, and only for group C. Because in the case of group A, there is no question that if you give the vaccine correctly, you will have a protective effect precisely in the population which you are trying to see a protective effect for the conjugate.

DR. GREENBERG: Ms. Fisher.

MS. FISHER: Just one quick question. Is the reason that we cannot --

DR. GREENBERG: Who is the question addressed to? To Carl?

MS. FISHER: Yes. Is the reason that we cannot do clinical efficacy trials in this country because there is so little disease in this country relatively? Is that the overriding reason?

DR. FRASCH: That's the problem in this country. The underlying level of group C meningococcal disease or the endemic level tends to be quite low. We do have problems of what I would call focal outbreaks that Dr. Perkins mentioned. The problem is there is absolutely no predictability of where these outbreaks are going to occur and, therefore, we can't go to a population and immunize that population in advance.

If we could do that, then, yes, it might be possible to do a study in the United States. Without this predictability, it makes it very, very difficult to try to do that.

DR. GREENBERG: One last question at the microphone.

DR. GEBER: It's actually just a comment. I'm Antonia Geber from the FDA. I just want to point out that we have recently allowed a placebo controlled trial on which Pasteur Merieux Connaught discussed in Niamay Niger so that there are certainly ethical considerations. It was a much smaller trial. It doesn't address logistical issues of detecting disease that I think we have allowed.

DR. GREENBERG: Okay. I would like to call this discussion to a halt for now. We are going to

obviously I'm sure revisit some of these issues after lunch. We now have time for open public hearing. Is there anybody in the audience that wishes to make a statement? I see somebody there.

DR. MADORE: Thank you. I'm Dace Madore from Wyeth Lederle Vaccines. I think as many of you know, Wyeth Lederle has made a meningococcal prime 197 conjugate vaccine that has been in evaluation in infants over the last several years. As we saw in some of the data that was presented, actually George Carlone's slides, studies by Ray Borrows in the U.K., this vaccine is highly immunogenic in infants as well as other populations whether evaluated by ELISA or by the bactericidal assay.

Since we had some discussions about the various methods that are used, high avidity ELISA and the standardized ELISA, I was wondering whether I would be able to show some of the Wyeth Lederle data regarding the performance of our ELISA which I think is relevant.

DR. GREENBERG: I think that's -- short yes. Pick your best data. Representative but best.

DR. MADORE: Thank you. Thought Wyeth Lederle assay differs slightly from the ELISA methods that have been discussed previously in that we use

polysaccharide that is purified by the Lederle organization and not the CDC supplied material and it's what we consider our standardized ELISA.

It also varies from the CDC standardized in that we do not use high binding plates. This is data just to show in the adult population, on the left, these are recipients of polysaccharide vaccine pre and post immunization, that we get a very good correlation between the IgG concentrations generated by our ELISA and the bactericidal titer. This is using rabbit complement, I'll make the note.

Similarly, with recipients of the conjugate vaccine, we have a similar relationship. For the purposes of time, I'm not going to show infant data or other age groups clearly regenerating very high antibody levels and so we're getting similarly very high correlations.

What I would like to share with you is another potential difference that has not been discussed yet on why the ELISA may not perform well in comparison to the bactericidal assay in some of the previously shown data.

In some interlaboratory studies that we've participated in, there were two different sources of the polysaccharide that were utilized in the ELISA by

laboratory Y versus ourselves, laboratory X. One notes this is the correlation between the ELISA output between the two laboratories with adult sera. The dotted line is the line of equality.

Using the different source of polysaccharide we see a different relationship. In fact, we're seeing overestimation of antibody levels at the low end. When the Wyeth Lederle source of polysaccharide was shared between the two laboratories, essentially one got equivalent results.

The reasons that we believe that there is some of the disparity between the laboratories can be brought out from this slide which is Wyeth Lederle polysaccharide that is used in both cases. In one case, the laboratory was using material that had been stored at four degrees and had acquired endotoxin levels.

Whereas, in the other case from the same lot of polysaccharide that had been stored frozen and freshly used, the same specimens were tested. These are adult pre-immunization sera. One can see that one does not get equivalence using these two antigens for the presera. However, on the next figure what I will show you is looking at post-immunization sera this difference is not as apparent.

This is the combined data from the pre and the post-immunization sera and I think it's similar to a lot of the graphs that we've seen presented earlier this morning. We believe that the presence of endotoxin can contribute to the behavior of these ELISAs and perhaps can account to what we are considering high avidity or regular avidity or broad avidity assays.

In fact, we have compared endotoxin levels and the standardized antigen that is provided by the CDC to the Wyeth source. There is about 1,000-fold difference in the presence of endotoxins. This may be a factor that contributes to the performance of the standardized assay as developed and standardized by the CDC. Thank you.

DR. GREENBERG: Thank you. Do any committee members have any questions about that presentation? If not, are there any other members in the audience who wish to address the panel? If not, there is one announcement and then we will adjourn.

I would like to speed things up a little bit here again just being a hurricane anxious person. I'm going to ask the panel to take 45 minutes for lunch rather than an hour so to be back here at 1:00 rather than the stated 1:30. Then we'll catch up a little

bit. I'm told by Nancy that we have space reserved for us in the downstairs restaurant to speed your ability to take feedings. We've tried to expedite that. If everybody could be back here at 1:00 sharp, we'll get on with our general discussion.

(Whereupon, off the record for lunch at 12:19 p.m. to reconvene at 1:00 p.m.)

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

1:08 p.m.

DR. GREENBERG: Take you seats. Is Carl here? Carl. If people would take their seats, we are going to get started here. We are now 20 minutes earlier than I had hoped to be and I figure we can be 10 minutes faster so I would love, if possible, to end this meeting at 2:45 as opposed to 3:15. If we can't, we can't but that's my goal. That means everybody has to think clearly.

Carl, you are going to reintroduce the questions.

DR. FRASCH: Thank you. What I would like to do is simply place the questions back on the overhead projector for everybody to look at and I'll go back to my seat and answer any questions you may have for me there. Thank you.

DR. GREENBERG: Okay. What I will do is simply first read the question and then ask for comments from our panel members. Of course, if you have any question about the meaning of the question or the intent, you can speak to Carl.

The first question is can we use immunologic correlates to demonstrate protective efficacy of a meningococcal conjugate vaccine for (A) individuals

for which the current polysaccharide vaccine is licensed. By that Carl specifically told us he meant people over the age of two; and (B) for infants and toddlers below the age of two and for whom the immune response of the polysaccharide vaccine was less than protective.

DR. FRASCH: I would like them to be answered as 1(A) and 1(B).

DR. GREENBERG: Right. Okay. So do I have some discussion from or thoughts from panels members? Kathy.

DR. ESTES: Well, from laboring in the hemophilus issues, I think there are some correlates and some lessons that can be learned from that story but there are some differences as well. I think the data from the correlation of protection with bactericidal titers from the military experience really is beautiful and suggest that if using that assay, that if you have greater than one to four, there is protection. I think that is really an important piece of information.

What I'm really struggling with is how we can take that particular assay and apply it to the vaccine studies of polysaccharides and conjugates. I'm having great difficulty seeing how the current

assays seem to correlate with the functional assay which appears to be protective.

For instance, in the PMC study the ELISAs seem to be very high but the bactericidal assays seem to not be very high so there seemed to be a real disconnect between the ELISA and the functional activity, at least in that particular study. Then I think I am also confused about the different sources of complement and is there going to be something that we can easily translate?

It seems that there are correlates of protection that have been clearly established but how we are going to use those correlates with the assays that we currently have remains very problematic and confusing to me.

DR. GREENBERG: Just as a point of clarification, in theory we currently have the assay that was employed by Dr. Gotschlich more or less for those very nice correlative studies. That is the human complement bactericidal antibody assay.

Dixie.

DR. SNIDER: I have a question I meant to ask earlier but there wasn't time. If I understood some of the presentation correctly, the antibody levels against bactericidal group A, C, whatever, go

up with age so that once you get in your thirties or forties a high proportion of the population have antibody levels.

How would you characterize those who have looked at antibody levels characterize the antibodies in those people who are naturally immune to the ones that have been actively immunized? Is there anything quantitatively or qualitatively different about the antibody responses?

DR. FRASCH: Well, again, the correlation was not for antibody levels with protection so much as the presence or absence of detectable bactericidal activity as measured invitro assay.

I think if people are coming from the hemophilus story where they had .15 correlates with immediate immunity, one microgram correlates with long-term immunity and that's even up in the air at this moment. I think there could be a problem because there really isn't good correlates with the amount of antibody as much as with the functional correlate.

If you are asking for an exact amount, we just don't have it from the standpoint of quantitating micrograms of antibody.

DR. SNIDER: Okay. I guess it's just another little piece of information if you are trying

to stack up an argument for using a correlate as opposed to disease. That was implicit and I think could be made explicit. That is, functional bactericidal antibody activity increases with increasing age in the population and that correlates with the decreased risk of hemophilus disease.

DR. FRASCH: And meningococcal disease.

DR. SNIDER: I meant meningococcal.

DR. FRASCH: I think the data that Dr. Gotschlich presented at Ft. Dix, there was not a single case of meningococcal disease among those individuals who upon their arrival at training at detectable bactericidal antibodies. Every case of meningococcal disease that occurred in that company occurred in those who were unfortunate enough at the moment of entry to not have bactericidal antibody.

DR. GREENBERG: I'm just going to ask one follow-up here. Were there cases of invasive meningococcal disease or meningitis in the polysaccharide studies that have been looked at and bactericidal levels done on those people retrospectively to know whether one can better get a handle on correlates of protection in the polysaccharide vaccine era?

DR. FRASCH: Emil, do you have a comment?

DR. GOTSCHLICH: Are you suggesting the examination retrospectively of vaccine failures?

DR. GREENBERG: Yes.

DR. GOTSCHLICH: I don't quite see how I would get any information out of them following the disease.

DR. GREENBERG: No, not following the disease. Prior to the disease following vaccination.

DR. GOTSCHLICH: Oh, I would have to have a serum available on an individual who was going to be a vaccine failure.

DR. GREENBERG: Well, I don't know. If you drew large numbers of serum. I don't know. Those studies were done before I ever even thought about meningococcal vaccines.

DR. GOTSCHLICH: No, that's not available.

DR. STEPHENS: But I think there is a broader issue and I would like to involve the participants or presenters in this question, a broader issue of a correlation between serum bactericidal activity. We've heard today about the relationship with natural disease, but I think there is also reasonable evidence that correlates with vaccine efficacy. Would anyone want to elaborate on that point which is, I think, one we really haven't fully

addressed.

DR. FRASCH: I think to take your point a little bit slight tangent, that is when there was an outbreak occurring in an African village and they administered the meningococcal group A polysaccharide, within 10 days of administration the disease had virtually disappeared. The only intervention, of course, was the administration of a purified polysaccharide. That means that induction of antibodies to the purified polysaccharide is sufficient to protect. The increased antibodies is correlated with the increase in bactericidal.

DR. STEPHENS: And that's also true in the group B outer membrane protein trials to my recollection where SBT was correlated with vaccine efficacy. Is that not correct?

DR. FRASCH: That's true. However, in the same study the ELISA --

DR. STEPHENS: I think it's important to separate the ELISA issue from the SBT issue because I think, unfortunately that's --

DR. FRASCH: I consider ELISA a further step away from protective immunity.

DR. STEPHENS: I agree with you. I think that's right.

DR. GREENBERG: Dixie.

DR. SNIDER: I mean, the generic question of can we use immunologic correlates to demonstrate protective efficacy has to be yes just based on our knowledge of biology. You really have to go beyond that question and say what are those correlates.

What we are hearing, I think, is that certainly there is an association between protection and the presence of functional bactericidal antibodies. We would presume because of biologic plausibility, etcetera, that there is a causal association there, although there are a couple of little answers to a few questions that didn't nail that down solidly as much as we would like.

There are also issues raised so that people were suggesting that we needed to have more than one immunologic measure. They were suggesting bactericidal activity as being very important. They are also talking about looking at high affinity antibodies in ELISA tests.

George, I think you are the one who mentioned opsonozation phagocytosis as another potential measure. I think for all of these there were also concerns about multiple tests and multiple methods of doing the tests and doing them in different

laboratories using different reagents. Although we heard the word standard several times, those were all different standards. There is some lack of clarity about what the standards would be for any one of those tests.

DR. GREENBERG: Thank you, Dixie. I would just like to make sure the committee is focusing on that first question. Just to slightly spin it a little different way, it wasn't do we believe that immunity is involved in meningococcal and prevention of meningococcal disease. I think if that was the question, we would have had a resounding yes. But it is can we use immunologic correlates to demonstrate protective efficacy of a meningococcal conjugate vaccine. That's the specific question. Not should there be but can we today take some correlate and use it to demonstrate efficacy. I think that is what the question is, can that be done. To answer that you would have to say how it would be done.

DR. FRASCH: Clearly the word is correlates. We didn't say correlate so, therefore --

DR. FAGGETT: Go ahead. I'm just next.

DR. FRASCH: So what I'm trying to say is we are talking about one or more immune correlates. For example, when we were trying to approve additional

hemophilus conjugate vaccines, we actually had a list of four or five immune correlates that we had to compare the new vaccine to.

DR. GREENBERG: Walter.

DR. FAGGETT: Yeah, just to clarify. Are we sure that they really want to ask the question of demonstrating protective efficacy? It might be better stated to predict protective efficacy. The discussions I've heard this morning have clearly shown the difficulty of having any kind of study to prove protective efficacy.

DR. GREENBERG: Carl, I actually agree with Walter that predict would be a better word there. Do you feel comfortable with that in question 1? Can we use immunologic correlates to predict?

DR. FAGGETT: Especially in this climate where we as clinicians are going to have to be convinced and meningococcal is a good example of where we are the ones that have real questions about how effective it is. If we are going to have folks buy into it as an FDA approved approach.

DR. FRASCH: I agree. We think there is a cause and relationship but, again, proof is a little difficult to come by.

DR. GREENBERG: Dr. Daum.

DR. DAUM: Just to clarify the question again. Do you mean that question should have the word existing in it or any generic? In other words, in the question can we use existing immunologic correlates or is the question do we think there is some way of finding a correlate?

DR. FRASCH: I think we are really talking about existing correlates but we are not necessarily talking about existing assays. For example, there's been some discussion today about doing a bactericidal assay in three or four different ways. That's not what we are discussing. We are discussing, for example, is bactericidal antibody measured in the appropriate way. Okay? I'm not trying to say that we have exactly the correct assay conditions at this moment in time.

DR. GREENBERG: So I have several people. Ms. Fisher, Dr. Huang, and then somebody else.

MS. FISHER: I have to go back to the use of predict versus demonstrate. In order to license a vaccine don't you have to demonstrate efficacy? I mean, if we're talking about moving on to the next stage, I think we have to look at whether or not efficacy has been demonstrated versus only predicted.

DR. FRASCH: That's correct. I mean, the

regulations say it has to be shown to be both safe and effective. It's obvious there is some gray area in every study.

DR. GREENBERG: Also this question doesn't go to licensure. This question says can we use it to predict. It doesn't say that the FDA has the right to use this for licensure.

MS. FISHER: But won't these trials presumably lead to licensure? The data will be used to license?

DR. GREENBERG: I'm sure the people out there on the other side of the microphone will hope that is the case. Other? Alice.

DR. HUANG: I would just like to follow up with what Dixie had initially said. I agree with him that I think what we have seen today if you take the data as a whole, it's very clear there are correlates and that we are not talking about efficacy. That isn't to say that we are talking about all the methods that would run naturally in the cure or recovery from disease. I find that for sentence No. 1, (A), it seems to require a yes.

DR. GREENBERG: Other panel? Dr. Daum.

DR. DAUM: I would like to ask Dr. Gotschlich to help me again because I didn't quite get

it before. In the Brazilian trial, the data that you presented this morning, I guess I'm getting a little hung up on the fact that the antibody concentration in children who are not protected looks to me almost like the same number, the same mean as those that were. I have a little trouble deciding that we have a correlate when those data are out there.

DR. GOTSCHLICH: Okay. First of all, I completely agree with you that this apparent paradox exist. What I tried to do this morning was to paint a picture that with the group C polysaccharide which engenders only antibodies to the group C polysaccharide you could define an age group in which this material is effective. If the vaccine is 90 percent effective in the age group of six months to five years, or in another study more or less 90 percent effective in an age group of two years to five years, then it is my conclusion that the immune response of the five-year-old must be protective.

Furthermore, I chose as the other side, in other words, to give you a lower limit of where protection might even be at least faintly evident to present you the Brazilian one. That would give you the marginal response that you would certainly wish to set standards above.

One could set standards but the conjugate vaccines should do what they do in U.S. military recruits. It works great. I think that would be a standard that is unobtainable at this point in time and is not realistic.

However, I believe if we look at the data and we separate the sheep from the goats in the conjugate vaccines, we will find a conjugate vaccine that will produce the immune response of a well-protected population with the group C polysaccharide itself.

DR. GREENBERG: Can I ask for a quick clarification, Carl? Are we talking here when we say efficacy of meningococcal conjugate vaccines, are we talking about group C or are we talking about all meningococcal vaccines? Most of our data has been group C here.

DR. FRASCH: We are talking about meningococcal vaccines.

DR. GREENBERG: Okay.

DR. FRASCH: However, it's obvious that the vaccine that the FDA is going to have to deal with is going to be primarily a meningococcal C vaccine or the 4 valent vaccine but we are not going to deal with meningococcal A vaccine by itself.

Relating to Dr. Daum's comment, I think he's talking about measuring antibodies by a quantitative way versus a functional way.

Now, this slide shows that if we had chosen to only look at ELISA we couldn't sort out a two-year-old from a 19-year-old. However, if one went to the functional assay, there are very striking differences between a two-year-old and a 19-year-old. Therefore, I don't think we should get hung up on trying to quantitate an antibody via ELISA.

DR. GREENBERG: Do I have some other questions from the panel? Dixie.

DR. SNIDER: Just to get back to an issue that you raised earlier to make sure it is dealt with or off the table. Implicit in question No. 1 is that we have already answered question zero, I guess, which is should we use immunologic correlates. I don't want to dig back and go over old ground again but it sounded as if we hadn't completely shut the door on the notion of using our standard approach, the randomized controlled clinical trial.

I would just for the record would like to say that what I believe everybody would say, that if there is an opportunity to do that, this use of feasibility and the money and the ethical issues and

so forth, could be dealt with. I think all of us would prefer data from a randomized control trial to demonstrate protective efficacy.

If it is decided that those conditions cannot be met, then it seems to me that we are left with having to use immunologic correlates if we hope to have new conjugate vaccines on the market.

Therefore, I think it is appropriate to change, demonstrate, predict for those reasons, as Walter had said, realizing that when we take a step away, we take some risk and the probability of our predictions diminishes somewhat when we have to work with immunologic correlates in situations like this where we have not nailed down the perfect tool to measure protective immunity.

I think the answer, in my view, could be yes for 1(A). We haven't talked about 1(B) yet. For 1(A) it would be yes, we can do that, but we will reduce the probability will be correct by some amount that I cannot articulate.

I'll ask for some more comments but I would like just before we go any further for people to limit their comments to Dixie, the first half of his statement, which I feel very strongly about as well and that the zero question, which is really not on

here, that I got the sense from around this table that given all the caveats and we can't go through all that now, by far the preferable way to determine efficacy of a meningococcal vaccine would be efficacy.

And that should remain and no stone should be left unturned to explore that even though we think it's very hard to do and that should always be the bar we see in front of us because we all have anxiety about these correlates.

Does anybody have any comment in that area? Diane.

DR. GRIFFIN: Well, the other advantage -- there are lots of advantages obviously to getting that kind of data but the other thing that it seems like we are lacking that makes this such a difficult issue is that we don't have even a set of sera from people in two different groups, one of whom didn't get the vaccine or got a vaccine that didn't work versus one that did that we can say what's the difference and really tease out what's the specificity, what are the biologic functions of that antibody that's protective.

We don't have anything we can go back to that has that. If we could get that but I guess there is nothing available from the original trial where the currently licensed vaccine. We don't have a set of

sera there that could be used or something that would allow us to feel much more comfortable that we have that correlate.

DR. GREENBERG: I have a number of questions here. Alice.

DR. HUANG: Well, just going back to where you were focusing on that I believe we all support the gold standard of a placebo controlled trial if that is at all possible.

DR. GREENBERG: Dr. Granoff.

DR. GRANOFF: Just one quick comment and that is the meningococcal polysaccharide vaccine was clearly shown to elicit protective antibody responses in adults. The conjugate vaccines after several doses are given as good or better antibody levels than those seen in the adults getting the vaccine which is shown to be protective. I think there may be situations where a placebo controlled trial is needed.

The second point is you can look at the -- we heard this on an animal model and primates but you can look at the ability of serum antibodies to passably protect against challenge in infant rat models. It is a way of looking at them.

DR. FRASCH: But from the standpoint of specificity the only antigen they are getting is a

purified polysaccharide and the disease disappears. I don't think there is an argument about the specificity. Maybe there is an argument how much antibody but I don't think there is an argument what the antibody is against.

DR. GRIFFIN: Well, there may not be an argument about the polysaccharide but there are probably many epitopes on that polysaccharide. Maybe that's incorrect. Maybe they are all equally applications.

DR. GREENBERG: Dr. Gotschlich.

DR. GOTSCHLICH: The question that Dr. Griffin raised in regard to not having a collection of sera with which you would have both efficacy and current serological techniques is one that bedevils me as well. That is precisely why I cast my discussion in the way that I did.

In other words, I tried to demonstrate that generically the vaccine works in five-year-olds anywhere and that generically five-year-olds anywhere respond more or less the same way. I believe that your anxieties can be allayed by accepting that.

DR. GREENBERG: I actually have a little concern with that reasoning because there is a failure rate in five-year-olds and I would really like to know

that failure rate was associated with a lack of response in that individual because, you know, all five-year-olds are five. Being five doesn't necessarily protect you.

It's a common trait of all five-year-olds. You're simply saying they all got vaccinated and they all have a generally high level of antibody. Therefore, if you get this level of antibody, you are protected. You really need the negatives in that to nail that down. You need to look at people who are not protected who don't have your levels of antibody to really prove that those levels of antibody in that protected population are the cause of that protection it seems to me. Dixie.

DR. SNIDER: I just wanted to follow up to clarify a little bit after Dan's comment. The one reason for preferring randomized control trials over these other possibilities, and even I'm glad to know that there may be an animal model and I think we would all like to see that be part of what is done to demonstrate that the human antibodies can protect the infant rat against challenge.

Doing the controlled clinical trials doesn't just answer the question does it work. It answers some other important questions like how well. What

level of efficacy are you going to get. That becomes important to convey to recipients of the vaccine. That becomes important to policy makers who have to decide whether or not to purchase the vaccine, etcetera. Again, I will stay say, yes, we can do it without it but there are still some reasons to prefer it.

DR. GREENBERG: Other questions? Dr. Breiman.

DR. BREIMAN: And also I think they give you the ability to answer some of these questions. I mean, you can appropriately set up studies and make it more possible given current techniques to derive correlates. I guess I would say, though, that at some point we are going to have to use correlates because given the difficulty of doing these trials and the number of potential vaccine products out there, it's difficult to imagine doing trials with all of these vaccines. At some point we are going to need to rely on a correlate.

DR. GREENBERG: Dr. Karzon.

DR. KARZON: When I read the sentence under No. 1, my immediate reaction is for what purpose am I agreeing with this statement. I agree with many of the things that have been said.

The correlates of protection as defined in the various versions of it that were presented were fairly persuasive and I would like to test them. However, I want to know what I am enabling if I vote for No. 1.

I still am stuck on the idea that I would like some further evidence of quite exactly how this does or doesn't work. I'm sitting here thinking about such opportunities and the studies that were represented by the CDC. For example, high risk houses of first-year freshmen comes to mind. Another possibility is containment vaccine has been used if we see one case to vaccinate all logical contacts.

I wondered whether something can be put together in which it would have preliminary use to test the hypothesis that given that the tests are done under appropriate control, that we do have a predictor of efficacy. I would feel most comfortable if we can head in this direction and get a little bit more data and answer a few other questions that have been floating around about different age groups and the experiential pattern as we go through the ages of what sort of protective material they are generating as they grow up and what happens in the elderly to reverse that trend.

DR. GREENBERG: I assume that the containment or the containment strategy there is already an accepted policy when you use the polysaccharide vaccine. That would be a hard one to do. The freshmen in college, I guess, there may be a policy pretty soon that would make that one a hard one to do as well. Basically that is continuing to look under stones for ways to test this thing.

Do I have any other -- do I have a feeling that we are ready to -- well, let me just put Dr. Karzon's question directly to Carl and the FDA. To what ends are you asking this panel to say yes to this if we do? Because I think you need to be sure that you are hearing a lot of anxiety about saying yes if the yes is the imprimatur to do a bunch of serology and say we have an effective vaccine.

DR. FRASCH: I think the FDA is asking or is bringing this subject up at this point in time is that you understand it's very expensive to do clinical trials. Companies are coming to CEBER asking for advice. Now, we don't want to give them advice that will lead to a very expensive trial that in the end was, shall we say, barking up the wrong tree. I think it's very important that the industry manufacturers get a feeling for what the scientific community as

represented by the FDA advisory committee are feeling. Therefore, we can give the companies the best possible advice.

The issue before this committee had been that trials were very hard to do from a logistical standpoint, not from an expense standpoint, although they are related. I assume you don't want them to bark up the wrong tree in the other direction and do a serologic test and then not get a vaccine registered because we don't feel that it comes before this panel and we don't feel that efficacy is. It probably cuts both ways. Diane.

DR. GRIFFIN: I guess really what I came away with from listening to everybody this morning was that I don't think that necessarily we wouldn't have a serologic correlate that we could feel comfortable with. I don't think we have a serologic correlate now that we can feel comfortable with. I mean, I think what I would ask for is a whole lot more data on exactly what is being measured in these various tests.

The SBA, the cidal test, the functional test, is the one I certainly feel most comfortable with because it is a functional test. That doesn't mean that any of these others might not be equally good but I certainly was not convinced that we had the

data at this point to accept that.

DR. GREENBERG: So if I hear you right, if that word existing is in there, you have trouble with this question. If it's not in there, you have less trouble. Is that correct?

DR. GRIFFIN: Correct.

DR. GREENBERG: Dr. Carlone.

DR. CARLONE: May I respond to that, please? What I am hearing on this side of the table, and I just want to make sure that I have this correct. When we talk about appropriate serologic correlates, what we are talking about in the broad stroke, what we talked about today, is the SBA and the ELISA.

What I was concerned about today, and I certainly was part of that, was the confusion of the protocol. We gave you three different protocols potentially for the ELISA and two different protocols for the SBA. What I think the confusion is is that we have good correlates for protection. We may not have, if you will, an optimal protocol for those correlates.

I think that simplifies the process in my mind a little bit more. Trying to find out if we have the right correlate is much more problematic than trying to put the protocol of that correlate in sort of proper perspective for everyone to agree on.

DR. PERKINS: I wonder if the question of randomized control trials will be eclipsed by the availability of Phase IV data from the U.K.? They will start next month the use of three of the conjugate meningococcal vaccines you've heard about today in their routine program. We would hope that Phase IV data will become available within a couple of years.

DR. GREENBERG: Very good point.

DR. FAGGETT: I think we in practice are concerned that there would be an effort to substitute correlates for clinical trials. It would appear that controlled clinical trials is an opportunity for us as primary care -- I'm speaking generically -- for primary care providers to participate and get a first-hand feel for efficacy in their own offices.

I wouldn't want to lose that opportunity. I do hope that if there is more utilization, it won't decrease the amount of clinical trials that we have an opportunity to participate in.

DR. GREENBERG: I think we are moving towards -- I would like to begin to round up this discussion so Dixie. Hold on one second. I've got two up here and then Dr. Snider and then Dr. Stephens and then the gentleman in the audience.

DR. SNIDER: Well, I wanted to try to move toward at least expressing my opinion. What I am hearing is that because we are not in this business, we don't know how feasible it would be to conduct randomized control trials.

I think the FDA working with the manufacturers with other experts in the field would have to make a determination as to whether it is or is not feasible and ethical to conduct a randomized trial. I think all I'm hearing is that this is the gold standard and this is what we would like to see and we would like everyone to be as innovative as they can in thinking about how this could be done.

If, on the other hand, it is determined that just cannot be done, then the question becomes using immunologic correlates. What I took away is that there may be a question about using a single measure such as SBA despite the fact that I agree with Diane, it looks like the best one.

I took away a suggestion that was made earlier that we would use several correlates. And also picked up on the suggestion of using the animal challenge. As a member I would say that you convinced me it was impossible to do a randomized control trial.

But, on the other hand, you proposed several

immunologic correlates, an animal challenge experiment, and data from Phase IV in the U.K. that I personally would find that if -- I don't know what the results would be but if those results all supported efficacy, I would think that I personally would be willing to accept that as sufficient data under the circumstances to make a recommendation to FDA for approval.

Somebody from the audience and the Kathy.

DR. POLY: I am Lionel Poly from Chiron. I just wanted to make a couple of points. I'm not sure if I understood this correctly from the discussion whether basically we went to a point where we are asking for efficacy trials. I'm not sure whether we are asking for efficacy trials for conjugate vaccines only. I thought that was somehow pushed for efficacy across the board.

I would like to just recall that efficacy trials have been performed for A and C conjugate vaccines. Those were the basis for approval for A and C conjugate vaccines because they were shown to be efficacious. And correlates were used already by FDA to approve Y and polysaccharide vaccines.

DR. GREENBERG: Did you misstate or am I very confused? You said conjugate vaccines.

DR. POLY: No, no, sorry. I'm saying polysaccharide vaccines. No, sorry.

DR. GREENBERG: Boy is this panel out to lunch.

DR. POLY: I think the question -- so there is no question obviously for the polysaccharide vaccine because the efficacy has been established and the correlates have been established and already used. The question is conjugate vaccines that we know are giving better, earlier, and longer lasting immunity, I mean, can we use the same correlates. We are now saying we are not asking for totally brand new correlates. We've been using them in the past. That's the point I wanted to make.

DR. SNIDER: You meant longer lasting immune responses. We don't know about immunity. That's the issue.

DR. POLY: Well, immune response is measured by bactericidal antibodies by ELISA and those kinds of things.

DR. GREENBERG: Dr. Stephens.

DR. STEPHENS: Yes. Having thought about this organism and this disease process for awhile and dealt with some of these issues, I just want to say I look upon this as an improvement of a vaccine that

does work. The ACYW135 vaccine works. It works in military recruits. It works in adults in outbreak settings. It has proven efficacious. All the data we have and the nuances of the assays are a different matter, as George points out, but all the assays we have indicate the conjugates are going to be better and probably better in young children where these vaccines are sorely needed.

I think that should crystalize, at least from my perspective, some of this discussion because we're not dealing necessarily, from my perspective anyway, with a new vaccine. This is an improvement, in my view a significant improvement, over a vaccine that already has proven efficacy.

DR. GREENBERG: Kathy.

DR. ESTES: Is it possible through the use of the conjugates -- different conjugates in the U.K. to give supplemental funding to do sera surveys in the populations in the U.K. so that there could conceivably be some additional data about amounts of antibody that could be predicative of protection in that population or is that sample size too small?

DR. PERKINS: We haven't discussed the possibility of us providing funding to the U.K. but we are actively discussing the kinds of studies that

could be done during their implementation process with the hope that they will do a Phase IV case control study with nested immunogenicity.

DR. ESTES: Could that conceivably be a sort of caveat for their licensure in the U.K. for companies to provide funding for such important studies?

DR. GREENBERG: We're not the U.K.

DR. FRASCH: This is not --

DR. GREENBERG: I'm going to take a few more comments. I've spent more time on this than the others because I think we will be able to move through the rest of the questions a little bit easier. Just to remind the new members, once we have finished this discussion, then I'm going to poll each one and ask them to answer the question. Diane.

DR. GRIFFIN: So from what I understand from the Chiron comment and then sort of rethinking some of this, is that if you could get exactly the same process or a better response by whatever panoply of assays you would care to use as you currently can demonstrate in adults or people over five or people over two or whatever the current vaccine is licensed for, even though it might be considered too high a hurdle in some ways, at least it would be a hurdle

that if it were achievable, would it be acceptable I guess is one way of looking at that.

DR. GREENBERG: Is that a yes? That was a question, I think.

DR. GRIFFIN: It was sort of a question that, you know, is that one way of looking at this that what we would ask for are responses that are at least as good as what has been demonstrated for the currently licensed vaccines.

DR. GREENBERG: In adults.

DR. GRIFFIN: In adults with whatever assays we decide are the appropriate ones.

DR. FRASCH: That question we have already posed to the manufacturers. We basically said when you set up an immunogenicity study, we want to know how the conjugate can be forming basically in a younger age group compared to a somewhat older age group receiving a polysaccharide. Remember, we can't give the polysaccharide --

DR. GRIFFIN: To young people.

DR. FRASCH: -- to so young.

DR. GREENBERG: Last one or two comments. Dr. Daum.

DR. DAUM: Just to return to Dr. Stephens' comment. My response to it was that while he may be

correct for older individuals, for infants we don't have a working vaccine to compare a conjugate performance with. I would actually like to hear his response to that because while that logic might be persuasive for grownups, it strikes me as not being quite there for young infants.

DR. STEPHENS: If you believe the correlates that have been presented this morning, the SPT data, even to some degree the ELISA data, but certainly the SPT data, then this improved vaccine in my view will work in children.

Emil points out that the group A polysaccharide vaccine already has demonstrated efficacy in young children in terms of its immunological properties which are somewhat different from the serogroup C and other polysaccharide. I think, from my perspective, this is clearly an improvement and that for a group in which the currently available vaccine doesn't work. It isn't useful.

DR. GREENBERG: Dixie, this is the -- Dixie and Barbara, the last two questions and then I'm going to ask you to put your money down.

DR. SNIDER: Well, I just want to put this in for the larger perspective. I know that we're

sitting here advising the FDA about advice to provide the manufacturers and that the next step would be achieve licensure of the vaccine.

I think from a public health standpoint, and from the manufacturer's standpoint, actually we want to achieve more than licensure of the vaccine. We want to use the vaccine widely to prevent the disease outcome. The manufacturer wants to be able to sell more of the product, to invest in more R&D, to provide profits, etcetera.

We all have a stake in activities that take place beyond licensure. Some of the concerns and some of the issues around what is available has to do as much with steps beyond licensure as it does with licensure. It's correlated with both. I just want people to keep the whole thing in mind that in the end you are not shooting for a licensed vaccine but a utilized vaccine.

DR. GREENBERG: Ms. Fisher.

MS. FISHER: Well, I'm still troubled by the issue. I realize this will be a signal to the manufacturers that perhaps they can proceed without having to do the clinical trials that will demonstrate efficacy has been done with the majority of other vaccines that we have licensed for use in children.

My concern is that we don't have yet enough information upon which to answer that question. Since this is a very important signal that we're sending, perhaps it's premature right now to answer that question.

DR. GREENBERG: I think we can get to that in 1(B). I'm trying to move things along.

MS. FISHER: Okay.

DR. GREENBERG: I'm going to take one step at a time and I think we will revisit that when we hit 1(B).

One more comment.

MS. SULTON: Ann Sulton, Biologics Consulting Group. I'm just going to insert a little bit of history into this and draw an analogy to the licensure of the hemophilus vaccines for use in toddlers which was not based upon an efficacy study with that conjugate, but rather was based upon the efficacy study performed with the polysaccharide in Finland.

The way that we got that conjugate vaccine licensed for toddler use was by using immune correlates direct comparison with polysaccharide vaccine in showing that immune response was equal to or better. That was not the case for the infants,