that's dominant in New Zealand.

And in these isolated island populations, they'll probably work. But we yet have no real answer for continental populations.

MEMBER MARKOVITZ: Are there problems with side effects also if it's so close to neural proteins?

DR. DECKER: Well, one simply doesn't do it. There are no polysaccharide-based vaccines for B because of this.

CHAIRMAN OVERTURF: Dr. Stephens?

MEMBER STEPHENS: As you suggest, one strategy may be to give this vaccine to 11 or early adolescents with Td. And I was interested that there looked like there was some significant difference between the immune response with concomitant Td and Menactra.

Can you comment on those data?

DR. DECKER: Different response in what way?

MEMBER STEPHENS: It was an enhanced immune response. When you gave Td with Menactra, the geometric mean titers were significantly or at least

appeared to be significantly elevated as opposed to Menactra without Td.

And it looked like you were getting some additional booster effect of Td in that kind of setting.

DR. DECKER: Well, remember Menactra is a diphtheria conjugate vaccine so when one administers Td, in essence one is administering an additional dose of the carrier in the other arm. And I think what we're seeing is carrier enhancement here. And, therefore, an increased antibody response.

And it goes both ways. The concomitant administration probably augments the antibody response to each vaccine.

DR. OVERTURF: We'd like the members of the committee to have their seats again so that we can resume, please. At this time I'd like to invite Dr. Lee to the podium to begin the review of the Clinical Safety and Efficacy for the FDA.

DR. LEE: Good morning. I'll be presenting FDA's Clinical Review of Aventis Pasteuris tetravalent meningococcal conjugate vaccine. I will

first present the proposed basis for licensure in ages 11 to 55 years old. Next, I will focus on four studies presented earlier today, MT02, MT09, MT04, and 12, and the primary data submitted in support of efficacy, safety, and concomitant vaccine administration with Td. I will then present the questions and the discussion points for the committee.

The approach to licensure of Menactra was based on the demonstration of immunogenicity and safety through non-inferiority comparisons to Menomune, a U.S. licensed meningococcal polysaccharide vaccine. These non-inferiority comparisons were a means of demonstrating immunologic and safety equivalents to Menomune. Licensure was also based on the demonstration of lot consistency.

Efficacy was inferred from an immune correlate rather than directly measured from a clinical disease end-point. As reviewed by Dr. Frasch, induction of bactericidal antibody following meningococcal vaccination has been shown to be protective, and thus this immune measure is considered a useful predictor of vaccine effectiveness.

Clinical efficacy of meningococcal A and C monovalent and AC combined polysaccharide vaccines have been confirmed in large scale field trials. In studies MT02 and MT09, bactericidal antibody response was measured with an assay using baby rabbit complement. Group C meningococcal antibody titers, however, reported from recent studies in the United Kingdom were found to be elevated when baby rabbit complement was used in the bactericidal assay relative to results using human complement.

Historically, bactericidal antibody results generated with an assay using human complement are most closely linked to individual susceptibility to meningococcal disease, but large volumes of human sera that are a suitable source of exogenous complement are not readily available today.

The sponsor was thus asked to test sera in a subset of study participants to determine the similarity of Menactra bactericidal antibody responses compared to Menomune when each of the complement sources was used in the assay. A similar immunogenicity profile with the two vaccines would

provide reassurance that efficacy estimates would also be similar.

In MT02, pre and post vaccination sera was obtained from 84 Menactra participants, and 81 Menomune participants. Sera was also obtained in MT09 from 50 participants in each group. Data generated from each assay was provided for sera groups C, Y, and W135 from MT02 participants from whom sufficient sera was available. And likewise, for W135 and Y in study MT09. Sera from a separate subset of 102 MT02 participants was used for Sera Group A analysis.

The antibody response was assessed by reverse cumulative distribution curves, seroresponse, and seroconversion rates. These reverse cumulative distribution curves represent post vaccination antibody results from a subset of Menactra and Menomume participants 11 to 18 years old with the serum bactericidal assay using baby rabbit complement.

For Serum Group C, 100 percent of Menactra participants achieved a titer of at least 1 to 8, and 92 percent achieved a titer of at least 256, compared with 100 percent and 95 percent respectively in the

Menomune group. Likewise, for Sera Groups A, Y and W135 the reverse cumulative distribution curves for the two vaccines were overlapping.

When the same sera was tested using human complement in the assay, the reverse cumulative distribution curves for each sera group were again overlapping. The sera response rate using baby rabbit complement was defined as four-fold or greater increase in antibody titer post vaccination compared with baseline. The proportion of sera responders was the primary endpoint in the two main immunogenicity studies. Here the sera response rate in the Menactra subset showed general agreement for each sera group except for Sera Group Y. For Sera Group Y, the 95 percent confidence interval for the difference in the two proportions do not include zero. However, the sample size was not large enough to draw definite conclusions.

The sera response rate using human complement also showed general agreement for the Menactra and Menomune groups. For each subgroup, the rate was 90 percent or greater in both vaccine groups,

except for Sera Group C in the Menomune group, which was 86 percent.

The seraconversion rates in adolescents using a baby rabbit or human complement source was also similar. And likewise, the immune response in adults using the same immunogenicity parameters was also similar.

Menatra and Menomune bactericidal antibody response with each complement source supported the same conclusion. The reverse cumulative distribution curves representing post vaccination titers in the two vaccine groups overlapped when either baby rabbit or human complement was used. Sera response and seraconversion rates were also similar, as well as the immunogenicity profile in adults.

Similarity of the immune response for the two vaccines with each source of complement, thus supported analyses of antibody response by baby rabbit complement in the larger immunogenicity cohort.

I will now discuss the two immunogenicity studies in greater detail. Studies MT02 and MT09 were designed as randomized modified double blinds due to

the different routes of administrations, multi-centered active controlled trials. Enrollment in MT02 included participants 11 to 18 years old, and in MT09, 18 to 55 years old. A single dose of Menactra or Menomune was given and serum samples were obtained at baseline and 28 days after vaccination.

The primary end point was the proportion of sera responders defined as participants with a four-fold or greater increase in bactericidal antibody titer 28 days after vaccination compared with baseline for each sera group. Other measures of immune response included bactericidal geometric mean titer, seraconversion rate, and group-specific igG and igM measured by ELISA.

The primary hypothesis was to demonstrate that 28 days after vaccination Menacta was non-inferior to Menomune. In MT02, the hypothesis would be supported if the upper limit of the one-sided 95 percent confidence interval of the difference in the proportion of sera responders was less than .1, which was equivalent to a 10 percent difference.

Subsequent to the conduct of study MT02,

CBER preferences for using a two-sided 95 percent confidence interval in non-inferiority hypothesis testing evolved to be consistent with the FDA's Center for Drugs and the European Union. This change was reflected in the primary hypothesis for study MT09.

The results of the primary immunogenicity analysis for MT02 are shown here. For Sera Group Y, the sera response rate in participants 11 to 18 years old was greater than 80 percent in both vaccine groups. And the rate was greater than 88 percent for C, A, and W135. For the difference in the two proportions, a negative value indicated that the sera response rate was higher in the Menactra participants than in Menomune participants for any of the four Sera Groups. The upper limit of the one-sided 95 percent confidence interval for the difference in the two proportions was less than .1, which was equivalent to less than a 10 percent difference for each Sera Group. Likewise, the upper limit of the two-sided 95 percent confidence interval was also less than .1. The primary immunogenicity hypothesis was thus achieved even by the more stringent of the two statistical

criteria.

In study MTA09, the prevalence of baseline antibody titer increased gradually with age. For Sera Group Y, the response rate in participants 18 to 55 years old was greater than 74 percent in both vaccine groups, and the rate was greater than 85 percent for the remaining Sera Groups.

The proportion of sera responders was higher after Menomune vaccination than after Menactra vaccination, resulting in positive values for the difference in the two proportions. The primary immunogenicity hypothesis was still achieved since the upper limit of the two-sided 95 percent confidence interval for the difference in the two proportions was less than .1 for each Sera Group.

I will now move on to the studies evaluating safety of Menactra. Safety information from six main studies and one supporting study were submitted in the license application. In total, these studies were comprised of over 7,000 Menactra participants, and over 3,000 Menomune participants. Characterization of the safety profile in ages 15 to

25 years old was felt to be important since the epidemiology of meningococcal disease in the U.S. and current ACIP recommendations for the prevention of meningococcal disease in college freshmen projected frequent use of this vaccine in adolescents and young adults.

For all Menactra and Menomune participants, detailed safety information was obtained which consisted of local and systemic adverse events and unsolicited adverse events within 28 days following immunization. Planned safety assessment after vaccination was included for four studies. At this evaluation, the participant was asked about visits to an emergency room, unexpected visits to an office physician, and the occurrence of serious adverse events. Ninety-six percent of participants from the four studies combined completed the follow-up evaluation.

In studies MT04 and MT09, these were studies that included a primary safety hypothesis. Both studies were randomized, blinded, multi-centered, active controlled trials. In MT04, 75 percent of

enrolled participants in each group were 15 to 18 years old, and 60 percent of MT09 participants enrolled in each group were 18 to 25 years old. Enrollment was stratified by age group to ensure adequate representation of adolescents and young adults.

The primary objective was to compare the relative frequency of a solicited severe systemic reaction among Menactra and Menomune recipients. Menactra was given intramuscularly, and Menomune subcutaneously. Since the routes of administration differed, study personnel administering the vaccine differed from personnel collecting the safety data.

Local and systemic adverse reactions were assessed daily for seven days following the vaccination, and the information was obtained by diary card and periodic telephone interview. The primary hypothesis was to demonstrate that Menactra was not inferior to Menomune in the proportion of participants with at least one severe systemic reaction during the seven-day period following vaccination.

The sample size supported the hypothesis

if the upper limit of the two-sided 90 percent confidence interval for the ratio of the two proportions was less than 3. The sponsor also included an analysis according to current CBER recommendations, which is based on the upper limit of the two-sided 95 percent confidence interval.

Hypothesis testing was based on the assumption that the expected proportion of Menomune participants with at least one severe systemic reaction was .01, meaning 1 percent.

The criteria that constituted a severe systemic reaction is shown here. Of note, headache, fatigue, chills, and arthralgia were considered to be severe if the participant felt that the symptom was disabling, required bed rest or analgesics. Any seizure was considered as severe, as was any rash occurring during the seven-day post-vaccination period. Rashes of interest in this category were lesions such as hives, purpura, or petechiae, since these rashes would be clinically significant, and rash had been included in post marketing surveillance reports for other meningococcal vaccines.

Since these rash descriptions were difficult to characterize for the vaccine recipient, all rashes were designated as severe in an effort by the sponsor to prompt the investigator for additional details regarding the rash, such as color, blanching or non-blanching, presence or absence of pruritus, and duration of symptoms.

The intent-to-treat population for safety included randomized participants who received one dose of vaccine, for whom safety information was available, and analyses were performed according to the vaccine received.

In MTO4 participants 11 to 18 years old, the frequency of pain and duration, redness and swelling was reported two to three times more frequently in the Menactra group compared with the Menomune group. The 95 percent confidence intervals between the two vaccine groups for each of these adverse events were not overlapping. Moderate reactions, including moderate pain, was also more common among individuals receiving Menactra. The rate of each severe local reaction, although more frequent

in the Menactra group, were all less than 1 percent.

In both groups, headache and fatigue were reported most often, and the rates were somewhat similar. Chills and arthralgia, however, were reported more frequently by Menactra participants. And for these two adverse events, the 95 percent confidence intervals between the two vaccine groups were not overlapping.

Fever defined as an oral temperature, 39.5 degrees Celsius or higher, was not a prominent feature in either group. And also, no seizures occurred in either group. Rash occurring during the seven-day post-vaccination period was reported by 51 participants. Fourteen participants reported localized rash either at or near the injection site, and 34 participants described the rash as non-specific, located on the extremities more often than the trunk, neck, or face. These rashes lasted a median of two days. Three participants reported generalized rash. One participant in each group described the rash as itchy, blanching, and which responded to Benadryl. A third participant received

Menactra and reported a generalized non-blanching red, raised rash that occurred two days post-vaccination and lasted four days.

In the primary analysis for MT04,all rashes were counted as severe, and for each reaction each participant was counted no more than once. The rate of severe systemic reactions in the Menactra group was .043, which was equivalent to 4.3 percent, and in the Menactra group and in the Menomune group the rate was .026 or 2.6 percent. The ratio of the two proportions was 1.7.

The primary safety hypothesis was achieved by the proposed criteria, which was the upper limit of the two-sided 90 percent confidence interval, and was achieved since the ratio was less than 3. The hypothesis was also achieved by current CBER criteria since the upper limit using the two-sided 95 percent confidence interval was also less than 3.

When rashes were excluded from the analysis, the percentage of participants with at least one severe systemic reaction was 2.7 percent in the Menactra group, and 1.2 percent in the Menomune group.

The ratio of the two proportions was 2.2. Of the study population which excluded rash, 1.1 percent of Menactra participants and .3 percent of Menomune participants reported two or more severe systemic reactions.

In both groups severe headache, malaise were most frequent. Although a higher percentage of Menactra participants had multiple severe systemic reactions, the difference was not statistically significant.

In MT09 participants 18 to 55 years old, the rate of pain in the study was similar in the two vaccine groups due to increased frequency of reported pain in the Menomune group, and duration and swelling were reported 1.5 times and 1.7 times more frequently in the Menactra group compared with the Menomune group respectively. The differences in these rates were statistically significant.

The rate of each severe local reaction, although more frequent in the Menactra group, were all less than or equal to 1.1 percent. Moderate pain was about three times more common among individuals

receiving Menactra when the study population was considered as a whole.

When the study population was divided into two age groups, pain was more discordant in the younger age group. Within the 18 to 25 year old cohort, moderate pain was reported four times as often in the Menactra group than in the Menomune group. And in participants 26 years and older, moderate pain was reported twice as often in the Menactra group. The rate of severe systemic reactions overall in participants 18 to 55 years old is more similar in the two vaccine groups compared with MT04. The rate of severe systemic reactions in the Menactra group was .038, and in the Menomune the rate was .026. The ratio of the two proportions was 1.5.

The primary safety hypothesis by the upper limit of the two-sided 90 percent and 95 percent confidence intervals for the ratio were again achieved by both statistical criteria. The percentage of participants with at least one severe systemic reaction when rash was excluded from the analysis was 2.6 percent in the Menactra group, and 1.9 percent in

the Menomune group. The ratio of the two proportions was 1.3.

Similar to MTO4 results, the percentage of participants with two or more severe systemic reactions was higher in the Menactra group than in the Menomune group, but the difference in the two groups was not statistically significant.

For the seven studies combined submitted in the license application combined, the overall rate of serious adverse events was 1 percent in the Menactra group, and 1.3 percent in the Menomune group. Pertinent events included two deaths, one death was reported in a 25-year old woman in a motor vehicle accident after Menactra vaccination, and the other in a 35-year old man who experienced cardiopulmonary arrest following drug overdose after Menomune vaccination. One event was reported by the investigator as possibly related to vaccination. This was a 17-year old Menactra participant with severe esophagitis who was hospitalized six days after vaccination. A plausible cause for the event, however, included a history of a sports-related back

injury four weeks prior to enrollment, and extensive and safe use thereafter.

Reports of anaphylactic and allergic reactions were uncommon. One Menactra participant had a prior history of a peanut allergy, and the other had a prior reaction to an antibiotic. Both participants reported symptoms after exposure to the same participants. The third Menactra participant an anaphylactic reaction after multiple bee stings. The recovery of all three individuals was uneventful. Reports of meningitis and pneumonia were also rare.

I will now move on to the study evaluating the concomitant vaccine administration of Menactra with Td. Study MTA12 included two groups, Study Group A received Menactra and Td concomitantly, then a saline placebo 28 days later. Study Group B received Td first, then Menactra. Enrollment included participants 11 to 17 years old. Antibody response to the meningococcal components was evaluated by the proportion of sera responders to each sera group.

The proportion of sera responders are shown in this slide as a percentage. In Study Group

A, when Menactra was given concomitantly with Td, the percentage of sera responders was greater than 85 percent for Sera Group Y, greater than 90 percent for C, and greater than 95 percent for W135. In Study Group B, however, when Td was given 28 days prior to Menactra, the percentage of sera responders for each of these sera groups was lower. The difference in the two proportions was 8.8, 20.7, and 8.7 percent respectively.

Similar to the percentage of sera responders, the meningococcal geometric mean titer 28 days after Menactra vaccination also showed differences in antibody response for Sera Groups C, Y, and W135. When an analysis was done to adjust for disparities in baseline titers, the difference in antibody response in the two vaccine groups was still noted. The effect of vaccine regime on antibody response was not easily interpretable without a direct comparison of each study group of adolescents to a group of adolescents receiving Menactra alone.

In the absence of this control group in Study MTA12, without making cross-study comparisons

and acknowledging the differences in study characteristics across studies could be different, definite conclusions could not be drawn about whether increased meningococcal antibody responses alone occurred when the two vaccines were given together, or if suppressed antibody responses also occurred in the group given Td prior to Menactra.

In the context of Menactra and Td vaccination, the safety of this vaccine regime was assessed from the perspectives of local pain rates, and any relationship between the frequency of adverse events to pre-existing antibody levels to diphtheria. The frequency of local pain at the Menactra and Td injection sites during the seven days following concomitant vaccine administration is shown here. Pain at the Menactra injection site was reported by 52.9 percent of participants, whereas pain at the Td injection site was reported by 70.9 of the same participants. Redness, swelling, and duration and pain was noted to be similar whether Menactra was given concomitantly, or in a sequential fashion.

From an alternative viewpoint, the

frequency of Menactra adverse events appeared unchanged by diphtheria antibody levels when Td was given with or prior to Menactra.

In both groups, the diphtheria GMT pre-vaccination was the same. However, 28 days after Td vaccination, the diphtheria GMT was 20.9 international unit per mil with the concomitant vaccine group, and 8.4 international units per mil when Td was given prior to Menactra. The diphtheria antibody level in the sequential vaccine group was consistent with diphtheria levels following routine TD vaccination in adolescents.

Hence, similar Menactra adverse event profiles, whether Td was given with or 28 days prior to Menactra, suggests that the frequency of adverse reactions are more related to the amount of diphtheria contained in Menactra than to the level of pre-existing diphtheria antibody.

In summary, the primary immunogenicity hypothesis to demonstrate non-inferiority of Menactra compared to Menomune were achieved for each sera group. The proportion of sera responders with a four-

fold or greater increase in bactericidal antibody titer 28 days after vaccination compared with baseline.

In MTA12, a difference in the antibody response to meningococcal components was noted in the group receiving Td prior to Menactra, and the group receiving Menactra and Td concomitantly. In the absence of a group receiving Menactra alone, these results were less easily interpretable.

Increased frequency of local and systemic reactions were observed in Menactra participants compared to Menomune. Although the percentage of Menactra participants with two or more severe systemic reactions was higher, the difference was not statistically significant, and the safety hypothesis to demonstrate non-inferiority of Menactra to Menomune were achieved.

I will now present the questions and discussion points to the committee. Question one - are the available data adequate to support the efficacy of Menactra, i.e., non-inferiority of the antibody response to Menactra compared to the licensed

polysaccharide vaccine Menomune when administered to individuals 11 to 55 years of age? If not, what additional data are necessary.

Question two - are the available data adequate to support the safety of Menactra when administered to individuals 11 to 55 years of age? If not, what additional data are necessary.

Discussion Point One - please discuss the adequacy of the data regarding the use of Menactra and other vaccines likely to be concurrently administered, e.g., Td. Discussion Point Two - please identify any issues that should be addressed in post licensure studies. Thank you.

DR. OVERTURF: Thank you, Dr. Lee. We will address the questions this afternoon, but at this time if there are questions of the committee for Dr. Lee on clarification of the data that she presented, I'll entertain them now. If there are no questions now --

DR. FARLEY: Monica Farley. You didn't mention, I don't believe, the lot-to-lot variation study, and I wonder if you -- there apparently was a

review of that, and do you have any comments on the -- did they achieve the goals there?

DR. LEE: As the sponsor mentioned this morning, there were -- the primary endpoint for a few of the sera groups was not achieved, and although the endpoint was not achieved, all the ratios of the GMT of the bactericidal GMT were all less than a ratio of 2. And so that the differences, while they were apparent, were thought to be less clinically significant.

DR. OVERTURF: Other questions? I think if there are no other questions, we will adjourn now, and plan to reconvene at 2:00 following lunch. Thank you very much.

(Whereupon, the proceedings in the above-entitled matter went off the record at 12:58:04 p.m. and went back on the record at 2:03:08 p.m.)

DR. OVERTURF: The afternoon session is beginning. Thank you. Before we begin the afternoon session, I'd like to introduce Dr. Karen Midthun who has an announcement she'd like to make for the FDA.

DR. MIDTHUN: Hello and good afternoon.

I just wanted to say that, as was mentioned earlier, this is the 100th VRBPAC Meeting, and as such, I'd just like to take a few moments to thank all of our members of the Advisory Committee, the public and all of the staff who have helped make this be a really good meeting time after time. And because of this, we actually have a cake that we ordered for this occasion, and at the break, please help yourself to a piece. So without further ado, back to serious business.

DR. OVERTURF: Next on the agenda is the open public hearing.

MS. WALSH: As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the committee. Dr. Overturf.

DR. OVERTURF: I'm required to read into the record a statement regarding open public hearing announcements. Both the Food and Drug Administration and the public believe in the transparent process for

information-gathering and decision making. To assure such transparency, the Open Public Hearing Session of the Advisory Committee Meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker at the beginning of your written or oral statement to advise the committee of any financial relationships you may have with the sponsor, his products, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any other such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

Our first speaker is Dr. David King, who is speaking as a New Jersey representative for the

Coalition for Mercury-Free Drugs.

DR. KING: First of all, my name is Dr. Paul G. King. I don't know who this other guy is, but that's who I am. And I'm speaking today on behalf of the American public and CoMeD. I have prepared a set of notes which I will diverge from fairly drastically, not because I wanted to, but because different information was revealed here than was in the packet that they provided, that the applicant provided.

I am neither affiliated with the government, nor any pharmaceutical manufacturer. My background is the area of CGMP regulatory compliance and sound science. I am a Ph.D. chemist with a Master's Degree in inorganic chemistry, and I am definitely not a vaccinologist. If you're interested in finding out about my credentials, my website is in the handout.

In general, my oral presentation will discuss Aventis proposed new vaccine from the viewpoint of a vaccine, and also the risk of reducing Mercury poisoning. Now one of the things I found out was that they did the study. They didn't compare it

to their vaccine they got approved, the approved Menomune vaccine, is a preserved vaccine, but they did it against their single dose vaccine, which is a low trace level Mercury vaccine, I believe. I guess I understand why. It might have got a lot more adverse reactions if you compared it against that one, so somebody is making a leap over a couple of hurdles that wasn't presented to this committee, because they presented this as if they were comparing this to their approved Menomune vaccine which they did by clinicals, and they're not doing that, which I find reprehensible. If somebody is going to do that, they should clearly have said that. We put this intermediate step in, and here is why.

By the way, I support doing that. I wouldn't have -- I would hate to have given any 18 to 55 year old or child a Mercury-containing vaccine at levels well above the toxic level, which according to Leong's work is on the order of oh, let's see - if you do the math, comes out to something like 4 times 10 to the minus 11 grams were applied to 2ML preparations of growing nurides, and 77 percent of them died. And he

tried Aluminum, Lead, Cadmium, and Manganese, and they didn't cause any deaths to speak of at all.

Now returning briefly to my remarks, the data on Menactra shows it's not worse than the Menomune single dose vaccine, and it does boost immunity, which the previous vaccine wouldn't do. So on that basis, I would probably support it as a vaccine for being approved. However, I have a very big caveat emptor.

With this vaccine, the sub titer varying shortly after vaccination less than 70 percent are protected, is this vaccine a preventive or is more indicator or discriminator? Does it simply ID those whose immune system can innately cope with this disease and blown its adverse effect to the mild or silent ones? Does it simply protect those who are not susceptible to the disease's severe effects? Perhaps these questions should be answered, because again, I would support it only to use just blunt outbreaks, or when you have populations of diverse people coming together, like in militaries or going to school where kids don't practice very good hygiene. I certainly

didn't my first year in school, and my university required me to live on campus.

The third thing I have a problem with is when we talk about going to extend this to doing it to children. Since the B subtype is not protected at all in the vaccine, I don't understand why you're going to give a vaccine that will, at best, initially protect less than, as I count it, 40 percent of the children inoculated, and after a year less than 20 percent. That's at best, and probably may not protect even that many. The cost of it doesn't seem to be beneficial.

The other thing I would point out is if you look at the history, Menomune has been around for a long time, and yet I don't see any drop in the outbreak rate, nor any real decrease in the death rate. So maybe again, it's like I said, it's only a vaccine. It's a good indicator of those people who are -- you give it to people and they don't get very sick with it, they are being who couldn't get sick with the disease very much. That's what I would say about -- that's what all I have to say about that, I would think.

Now the other thing which I worry about is that you say the strains vary and whatever, but as I read all the things I could get my hands on, which aren't very many, it seems that the vaccine has shifted the population of strains. And that may not be in the long term a good thing to do either, and that's another reason I'd recommend this be only approved for outbreaks or in situations where the potential of outbreaks is large, and not as a general vaccine to the general population.

Also, I noticed that these people failed to provide a risk benefit analysis, and I find that particularly reprehensible because the FDA says now everything is supposed to be based on risk benefit. In other words, here's what the cost is to the population, the risk - you know, the total risk, health effects, could of the medicine and whatever. Here's what the people who are going to get this, going to get as a benefit. If it really doesn't protect anybody but the people who would be protected anyway, maybe if it blunts the more -- it might be worth it in an outbreak sense, but at $80 a dose for

300 million people every three years, I think I'd have a hard time justifying that as being cost-effective healthcare. We could do much more better things just to get the kids to wash up better, practice better hygiene, clean their rooms and stuff better, and that would reduce the risk of anyone getting the disease in the first place.

As I've said before, nonetheless on balance, being forced to consider it less -- I would still support this vaccine being approved, provided the following actions are taken. There should be at least a five-year Phase Four trial where all the data is collected on all the people given it for five years afterwards, especially since you're going to be giving a booster dose after three years. It looks like you're going to give this as a vaccine in the normal sense of that word.

Also, I think if you're going to approve Menactra, you should certainly revoke the license for the Mercury laced or the preservative Menomune, if not both of those vaccines, because they're obviously inferior in that they do have an adverse effect if you

ever try to get re-vaccinated with the Menomune, even the low dose one.

Third, again I will re-emphasize, only approve for vaccinations of most seriously at-risk sub-populations; for example, incoming college freshmen who reside in dormitory settings, military conscript, volunteers in service, orphanage residents, nursing home or residential communities for the elderly. And for a similar reason, vaccination should be restricted to initial dosing and one booster dose at three years subject to review after five years experience under the Post Approval Surveillance Program.

And C, to prolong a rabies acquired internal immunity, DHHS should strongly promote breast feeding for not less than two years because in Mother Nature, that's what happens.

In closing, let me assure this panel that failure to truly consider these simple science-based requests and acting appropriately may further undermine the public's willingness to subject themselves and their children to vaccines that have

real cost and real risk to them for the sake of the purported benefits to the population as a whole. Because again with the babies' case, if you believe herd immunity requires 80 percent immunization, then there's no way you're going to get it by giving babies a Non-B vaccine when that's the majority sub titer.

Remember rather than trying to continue to increase the number of vaccines, the number of doses given to the point that bad vaccines - my favorite examples are Lyme disease vaccines and the Smallpox vaccine, in worst practices are incorporated into the vaccine schedule, the money would be better spent re-emphasizing the importance of personal hygiene and providing clean housing for the poor and the homeless.

For example, since bed bugs and not direct contact with a vector that transmits Smallpox, and with supportive medicines which we have, the death rate is under 10 percent, DHHS would be better off spending money on providing clean insect-free housing for the poor and homeless, and promoting the washing of bed clothes with very hot water and bleach, instead of trying to vaccinate the public and cause thousands

of unnecessary Cowpox reactions, and hundreds of unnecessary Cowpox deaths.

Finally, does the cost of one dose outweigh the potential maximum benefits per year? I don't think so. Thank you. Any questions, I'll try to answer them.

DR. OVERTURF: Thank you, Dr. King. Are there any questions for Dr. King? Thank you very much. Our next speaker is, I hope I have this right, Mike Kepferle from the National Meningitis Association.

MR. KEPFERLE: Thank you. My name is Mike Kepferle, and I'm one of the founding directors of the National Meningitis Association. We're at a non-profit health education foundation that tries to educate families, medical professionals, and just the general public about meningococcal meningitis, meningococcal disease, in particular, and the ways that you can help prevent it; which obviously include both immunization and good hygiene.

I want to say that we have been waiting. I'm a parent, and I represent a lot of parents that

have been impacted by meningococcal disease, and we have been waiting for something to change. Now we haven't been waiting passively. We've been trying to make things happen, but we look forward to this new conjugate meningococcal vaccine, if it's approved, because of what we hope that it will do to protect the children.

We're also waiting for a serogroup B vaccine, and I hope there's some discussion with the folks down in New Zealand about what's going on there, and the potential for a vaccine here in the U.S.

One Saturday I took my son, Patrick, who was 18 years old and dropped him off at college. Sunday he was dead. I couldn't even pronounce meningococcal, and I'd heard about Meningitis. In fact, we had received some information in 1999 in our college application that recommended he be vaccinated with a Menomune vaccine. But the wording of the recommendation was kind of hard to follow. It didn't matter. We're very pro vaccine. He had his Hepatitis vaccines, but we took him to a Navy clinic, which is where we were getting our medical help, and ironically

at a military base we couldn't get the Menomune vaccine for him. But we weren't worried.

We didn't know much about Meningitis, but we figured he'd just get a shot when he went to school, and we encouraged Patrick to do that. Well, he didn't do it the first semester, and so I remember distinctly besides telling him to get his grades up, that he needed to go to the health center and get the shot, and I'd pay for it. Well, in March he came home to watch his high school team play in the regional playoffs, and then went back that March 4th, 2000 - it's now been four years - it seems like yesterday, and he was dead on March 5th.

After that happened, I reached out to other parents who I know lost children. I found about it, and I learned a lot, and we started the National Meningitis Association. And if I could have every one of those parents sitting in this room, because there are more parents than would fit in this room, and I have to represent them because I'm the only one that could make it here, but if I could have them sitting here, they'd say please, please get us another

vaccine, and help protect our kids.

Now my son was in that classic college 18-year old freshman living in a dorm situation, but believe me, I've talked to a lot of parents that have lost kids that are 11, 14, 12. Last week, David Pasick, Wall, New Jersey died at 13 years old. I met with a family up in Washington State whose 12-year old son, Carl, had both of his legs amputated. And I don't think I need to tell most of the medical folks here what this disease can do, but I do want you to know that we parents that didn't know what this disease could do, and all of the parents out there that still don't know, no matter how much we try to educate them, need to be given a vaccine that is going to protect not just the college kids, but also the ones that are younger. And every child in this country that is eligible for a vaccine and can be protected by the vaccine should be given that vaccine.

All the families that are involved with NMA want you to know that we know that immunization and education are the only combination that are going to save our children's lives. And I don't want next

year to tell a parent of a 12-year old who lost their child because they didn't have a vaccine that could have saved their lives, that well, we're another year later, and I'm sorry. Because that's what I'm telling them right now, and I don't like it. So please, please get us the vaccine that we need, work with us to educate the public so that they know what the vaccine can do for it, and thank you. Do you have any questions?

DR. OVERTURF: Are there any questions for Mr. Kepferle? Thank you very much. Is there anyone else who would like to make a presentation during the open public hearing? If not, I will ask Dr. Carl Frasch to come forward and we'll begin addressing the questions for the afternoon.

DR. FRASCH: Okay. What I'm going to do is I'm going to go through two questions and two discussion points, and then be sure that there's a clear understanding of exactly what the committee is being asked. Then we'll go back to question one, and Dr. Overturf's open the questions for discussion.

So the first question is, are the

available data adequate to support the efficacy of Menactra, in this case as defined by non-inferiority of the antibody response to Menactra compared to the licensed polysaccharide vaccine Menomune, when administered to individuals 11 to 15 years of age. If not, what additional data are needed.

The second question and the last question for which the committee will vote is, are the available data adequate to support the safety of Menactra when administered to individuals 11 to 15 years of age? If not, what additional data are necessary.

Now the next two are discussion points. First discussion item is, please discuss the adequacy of the data regarding the use of Menactra with other vaccines likely to be used concurrently, administered concurrently. For example, Td. And the last discussion item - please identify any issues that should be addressed in post licensure studies.

So I would open the -- see if there's any discussion regarding the meaning of any of the questions. If the meaning of the questions are clear,

then I'll be finished. Okay.

DR. OVERTURF: If not, we'll go ahead and proceed with a discussion of the first question. The first question is, are the available data adequate to support the efficacy of Menactra, i.e., non-inferiority of the antibody response to Menactra compared to the licensed polysaccharide Menomune when administered to individuals 11 to 55 years of age. If not, what additional data are necessary? Are there discussions or questions? This is a question we will vote on, and what we will do at the time of the vote is to proceed around the room. If you have additional data that you think is necessary, regardless of what your vote is in that regard, you should state it at that time into the record. Did you have a question, David? No. Any other discussion regarding this question? This is a very quiet committee today.

This time I think we'll start with Dr. Karron, and ask her for a yes or no vote, and any questions regarding additional data that she feels is necessary.

DR. KARRON: Yes, I believe that the data

are adequate to support the efficacy of Menactra; that is non-inferiority of the response to Menactra compared to Menomune.

DR. OVERTURF: Dr. Self.

DR. SELF: Well, at risk of contradicting myself I will vote yes, I think the data are adequate. But I'll also say that I would like to see some more data, and that would have to do with the relationship between the antibody response and risk for other serogroups.

DR. OVERTURF: Dr. Densen.

DR. DENSEN: I believe the data are adequate to support the non-inferiority of the candidate vaccine to the current vaccine.

DR. OVERTURF: Dr. Whitley.

DR. WHITLEY: According to the standards specified by the Food and Drug Administration and Aventis, I believe that Menactra should be approved for efficacy.

DR. OVERTURF: Dr. Word.

DR. WORD: I would agree that there is adequate data to support the efficacy of Menactra.

DR. OVERTURF: Dr. Petteway, I believe you're a non-voting member for this. Do you have any comments that you want to make?

DR. PETTEWAY: Well, the only comment is I think it's clear, I think that the data does support non-inferiority.

DR. OVERTURF: Yes, Dr. Stephens.

DR. STEPHENS: I also agree the data are supportive that this vaccine is non-inferior.

DR. OVERTURF: Dr. Gellin.

DR. GELLIN: Also in agreement that the data as presented are in agreement with the -- supporting Menactra based on non-inferiority for efficacy.

DR. OVERTURF: Cindy Province.

MS. PROVINCE: Yes, I do believe that the available data are adequate to support the efficacy of Menactra according to the conditions that have been given.

DR. OVERTURF: Dr. McInnes.

DR. McINNES: I believe that the available data are adequate with regard to efficacy for

Menactra. I would like to see additional data on persistence of antibody so that one might better understand the possible priming, boosting. And I think data on the kinetics of the antibody response would be of great interest also in further understanding the biology of what is happening.

DR. OVERTURF: Dr. Farley.

DR. FARLEY: Yes, I think that the data do support the non-inferiority of the product. I agree that having more information on the subsequent dosing and boosting would be of great interest.

DR. ROYAL: I agree that the data demonstrate that Menactra is not inferior to Menomune.

DR. OVERTURF: I'm sorry. I didn't call Dr. Royal's name. That was Dr. Royal's vote. Dr. Markovitz.

DR. MARKOVITZ: Yes, I'd like to vote yes, that this has been demonstrated and strongly echo the comments of Dr. McInnes and Dr. Farley, that it's going to be very important to see that follow-up about boosting and antibody persistence, because I think that's what will ultimately make this a vaccine that

people will really want to use.

DR. OVERTURF: I also would vote affirmatively for this, but I think the data strongly support this. I think there is going to be needed data regarding persistence of antibody, and particularly persistence of protected antibody, and also when boosting will be required.

I also would hope very much that there would be -- that the data for children will be coming along very, very shortly, because I think that's going to be an important long-term component, probably controlling meningococcal disease, as well.

The second question is, are the available data adequate to support the safety of Menactra when administered to individuals 11 to 55 years of age? If not, what additional data are necessary? So this question is now open for discussion from any member of the committee. Are there questions regarding this? So a slightly different standard here because it's not truly a comparable vaccine. It has actually more antigenic components and, therefore, the non-inferiority is a little bit more difficult to apply,

because of the fact that you going to expect more reactions, which I think the sponsor addressed. Ye, Dr. Whitley.

DR. WHITLEY: I just think to reiterate that point, don't forget the two vaccines are given by different routes. One is given subcutaneously, and the other is given intramuscularly, and that does introduce a variable that needs to be considered.

DR. OVERTURF: Are there any further comments or questions, discussion? Well, this time we'll start with you, Dr. Markovitz, if you could address that question.

DR. MARKOVITZ: Yes. I mean, I think similar to what might be expected by the comments that Drs. Overturf and Whitley have made, this is slightly more reactogenic vaccine than is the currently licensed version. But nonetheless, I think it's safe. I'm convinced that the safety data are good. Because it's more reactogenic, I'd certainly want to see very close follow-up once people are vaccinated in larger numbers, so I would vote yes, for the safety issue.

DR. OVERTURF: Dr. Royal.

DR. ROYAL: Thank you. I would vote that the data do demonstrate that the vaccine is safe.

DR. OVERTURF: Dr. Farley.

DR. FARLEY: I would say yes, the data are adequate to support the safety of the new vaccine.

DR. OVERTURF: Dr. McInnes.

DR. McINNES: Yes, I found the data to be adequate to support the safety of Menactra.

DR. OVERTURF: Yes, Ms. Province.

MS. PROVINCE: I do agree that the data are adequate to support the safety of Menactra. And I just want to make a general comment for the record about the importance of post-licensure surveillance. That may be more appropriately addressed under the discussion points, but I think it will be very important to look at the safety data as it continues to come in, both for the adverse events that have been detected so far, and is of extreme importance, and continue to monitor this vaccine for even the possibility of rare adverse events that might not have been adequately detected pre-licensure. I think that that's just a growing issue involving public

confidence in vaccines.

DR. OVERTURF: Thank you. Dr. Gellin.

DR. GELLIN: Given the caveat stated about the differences in antigen content and the route of administration, I also believe that the safety data as presented are adequate to license this vaccine based on safety. And agree with Cindy that there's a need to have ongoing safety studies, particularly - and we'll get into this with the next question - with concomitant administration, and if this is a vaccine that is then given to children, where there are more vaccines administered.

DR. OVERTURF: Dr. Stephens.

DR. STEPHENS: I would agree this is, as the data suggests, this is a safe vaccine. I would also agree with the comment just made about concomitant vaccines, in particular Td concomitant administration where I think the reactogenicity issues may be even more pronounced. And other vaccines concomitantly given is of concern.

DR. OVERTURF: Dr. Petteway, do you have any comments?

DR. PETTEWAY: It's clear that the data supports safety.

DR. OVERTURF: Dr. Word.

DR. WORD: I think it does support the safety of Menactra.

DR. OVERTURF: Dr. Whitley.

DR. WHITLEY: I believe the vaccine's data support safety, but I want to contribute to the caveat that was made earlier; and that is, I think surveillance studies need to be in place when this vaccine is licensed recognizing that the total number of people who participated in the clinical trials were only 7,500. And by my standards, that's a bit slim in terms of understanding the safety profile.

Furthermore, we all know that once we go beyond clinical trials, what happens in the real world is very different. And so being able to monitor that, and reinforce public confidence is essential.

DR. DENSEN: I agree with my colleagues that the vaccine is safe, and I echo the comments of Dr. Whitley.

DR. OVERTURF: Dr. Self.

DR. SELF: I agree the data are adequate to support the safety of Menactra, and concur with Whitley and others about surveillance post-licensure.

DR. OVERTURF: Dr. Karron.

DR. KARRON: I agree that the data are adequate to support the safety of Menactra, and agree with others' comments about the need for post-licensure surveillance.

DR. OVERTURF: I also will vote affirmatively for the confidence in the data on the safety of Menactra. I also feel that with recent history as the test, that 7,500 patients sounds like a lot but it turns out to be a fairly slim number, particularly for those very rare adverse events, so post-marketing surveillance will be a critical part of this vaccine's future.

Now at this point, we're going to open up the discussion to the adequacy of the data regarding use of Menactra with other vaccines likely to be concurrently administered, such as Td. And we've already commented on Td. When and if we begin to extend this vaccine to much younger children -- yes,

I'm sorry. Dr. Frasch.

DR. FRASCH: I just want to clarify that concurrent doesn't only mean given at the same time as, but within reasonable proximity of, like a week or so on either side.

DR. OVERTURF: My comment would be that there are vaccines which are given in college health services, and are recommended. Often college students do not get the second dose of MMR until college. The other vaccine, which is a live vaccine, they also may not get vaccinated for Hepatitis A and Hepatitis B prior to college, and some of those are recommended, as well. So there will be a need for at least some additional data for safety and the effects on immunogenicity of this vaccine. So at this point, I'll open the question up for discussion, and see if there are additional comments by the committee members. Any additional comments? Dr. Word.

DR. WORD: I think you've mentioned a number of other vaccines that need to be addressed when you administer this, but it's not just that we're just talking about the adolescent population. You're

extending it out, and besides just routine healthy immunizations, you have to think about people who do participate in international travel. And there are a number of other vaccines that may be administered at those time periods, like Yellow Fever, Japanese Encephalitis. I mean, you're not going to need a lot, but when you're dealing with some of these adolescents particularly go out of the country, they go to missions. And also, I think Dr. Karron brought up the question about oral Typhoid, even though many of us don't use it as much, we use the injectable because of the conflicts occasionally with Malaria prophylaxis. There are some people who still use oral Typhoid.

DR. OVERTURF: Are there any other questions? There's actually a number of those travel vaccines, including for people going on extended stays in rural countries, Rabies vaccine, pre-exposure prophylaxis is recommended. Others receive dosing of things like Yellow Fever vaccine for certain kinds of settings, as well. So in addition to Typhoid and also the Hepatitis A vaccine that I mentioned, so I think there will be a number of the travel vaccines that

will have to be looked at.

DR. WHITLEY: Procedurally, Gary, what do we have to do? Do we have to make a formal statement for the agency on discussion items, since this is a non-voting item, or what do you want from the committee?

DR. OVERTURF: We do not have to have a vote. What's required here is a discussion for the sponsor and for the FDA to help direct them into studies that need to be done further for concurrently given vaccines.

DR. WHITLEY: Then I think we should make a definitive statement that the data regarding the use of Menactra plus Td, versus administration of Td followed a month later by Menactra need to be clarified so that the immune response, persistence of immunity, and kinetics of immune response are all identified under those circumstances.

DR. OVERTURF: I agree. I think also safety needs to be addressed in that regard. When the vaccine is given with some of these other vaccines, that's going to be necessary. Actually, the data

that's presented today I think we all would agree is very limited and only begins to scratch the surface with what's needed. Dr. Stephens.

DR. STEPHENS: I think there also needs to be some additional data about the use of this vaccine in individuals that have previously received the polysaccharide vaccine. We heard some data today and it hadn't been, as I understand it, reviewed by the FDA, but there was data presented, a little bit of data in that regard. But I think this is an important group, because a number of college kids, obviously, a number of the population have already been vaccinated with a polysaccharide, and we need to have some understanding, a better understanding of how this vaccine would be used in those groups, laboratorians, for example.

It's also true that there needs to be a better understanding of what happens when the polysaccharide is used after this vaccine. We didn't hear any data from my perspective, or I didn't hear any data about that today; although, I think that data does exist, and I think it may be an effective

booster. But some more data about the concurrent use or the previous use of polysaccharide vaccine in conjunction with this vaccine needs to be obtained.

DR. OVERTURF: Yes.

DR. WHITLEY: Can I just amplify on what Dave said for one minute. And I think it goes back to the question that I posed earlier; and that is, the day-28 data need to be extended far out. And I understand that data will be forthcoming in children, and you have it, but it should be also available in other populations, as well, because that will be crucial in terms of the people who just get Menactra, versus those who have the polysaccharide vaccine followed by Menactra.

DR. OVERTURF: All right. I think we'll probably -- the likelihood is that we'll be exposing a fairly sizeable large population immediately to this vaccine, particularly in the adolescent age group. And we don't know much past a few months, so I think that's where the critical early information needs to come from. Yes, Dr. Farley.

DR. FARLEY: I agree. I'm concerned if we

have a successful vaccine campaign of 11 year olds ,we will be uncertain what to be advising them to do when they're going to be college freshmen in dormitories, so I think we have a lot to learn for that very high risk population.

DR. OVERTURF: Is it fair to ask the sponsor if any of those kinds of studies are planned, with some of the initial populations that were immunized at 11 to 12 or 15 years of age. Are any of those planned for long-term booster studies? Just introduce yourself again.

DR. DECKER: I'm Dr. Michael Decker. I heard several issues raised that are closely related. We showed you the data from MTA19, which are being submitted or may have just been submitted to FDA for their formal review. And that involves a three-year follow-up with the cohort from the MTA02 participants. We're continuing to follow these children. One reason why it was a subgroup that was reimmunized there was to leave some children behind who could be evaluated, and potentially reimmunized at five years, or at successive time points. So it's our intention to

follow this MTA02 cohort on out. And remember now, they're a full four years ahead of the public that has not received the vaccine at all yet. So we recognize precisely the question was raised. In fact, to me that's one of the most compelling questions, is if we immunize a cohort of 11 year olds as I hear that ACIP is considering, the question will be raised when they approach colleges are they covered, do they need a booster? And so we have this cohort who were immunized at 11 years old already in the study, and the adolescents limit 18, but it includes -- it will provide data that will address this question. And you saw what it looked like three years out. We're waiting to see in about year, we're going to see what it looks like five years out, and so on. And so we have that going.

I don't want to talk much at all about the data for persons younger than 11, because that's not the subject of today's meeting, but I know it's of great interest to people. And we have done similar work in that group, and are following them on out. So I believe that we will have data that will directly

address the things that we all need to know.

DR. OVERTURF: Dr. Royal.

DR. ROYAL: I'd like to put in a plug for studies being pursued that might increase our understanding of the mechanisms that might be associated with any increased efficacy that might be seen going back to the comment about not only were the formulations different, but also the routes of administration were different, which makes it a bit difficult to understand whether it's the formulation or the intramuscular injection that's really responsible for the increased immunogenicity. So such studies may not necessarily involve humans, and it may be difficult to do in humans, but I would be very much in favor of them being done.

DR. OVERTURF: Another issue in mechanism might be also to look more closely at those sub-populations which actually have complement deficiency. That will be a difficult study, although at least in many populations, the estimated number of individuals who are deficient have those complement deficiencies vary from a 5 or 10 percent number, all the way up to

as much as 30 percent, depending which population you're looking at. It will be interesting to see what the immunology is in those patients who received those vaccines in that particular population, particular group.

DR. DENSEN: I have two comments, one just related to your last comment. I think the variation, the number of complement deficient patients in different populations depends on the incidence of meningococcal disease and the population in general. But in an endemic population, it runs pretty consistently about 10 percent.

I would like to encourage the FDA to organize studies that would look at the principles that might emerge when you give mixed vaccines, so you give this vaccine with another vaccine, so that we could understand whether or not there are general immunologic principles about combining vaccines that could be derived, or whether these combined administrations always represent unique events related to the vaccine properties itself. So that as we move forward, we would have a handle on some of the very

real questions that have been raised here, and we wouldn't have to solve that problem each time, if there are emerging concepts.

DR. OVERTURF: Dr. Word.

DR. WORD: Just a question - I guess I thought of it when you started talking about some of the people who have some complement deficiencies, but people routinely are recommended to receive meningococcal vaccine because of underlying health problems. Where will they fit in, because the wording here is just for individuals 11 to 55, and so many of them would be of the age where they're getting a booster, or if there splenectomized. I'm not quite sure how -- is it only going to be for healthy people? I mean, the way it's worded, it seems like it's for anyone between 11 and 55.

DR. OVERTURF: Well, I think the populations that were studied were healthy populations, so whether -- that actually is not really technically an issue for this committee.

DR. WORD: Okay.

DR. OVERTURF: How the vaccine is used,

and how it's recommended to be used once it's approved is for other agencies. And the point I was trying to make is that there does need to be additional studies of those populations specifically. Whether it will be used or not immediately is up to other groups. Dr. Stephens.

DR. STEPHENS: The real question is whether this is a better vaccine than the polysaccharide, and I think the data - we'll get to that probably in question four, but the real data is not there, in my view, that this is a better vaccine. We have a lot of promises. We have the experience in the U.K. with different vaccines. One of the hopes is that this vaccine will induce a herd immunity response, a significant herd immunity response. We don't have any data about that with this particular vaccine. I think very clearly we would like to - I would certainly like to see some data looking at mucosal antibody, looking at potential of herd immunity for this particular vaccine.

Sixty percent of the preventive cases in the U.K. were due to herd immunity, a very powerful

correlate, immune correlate of conjugate vaccine, certainly see with the pneumococcal conjugate, as well as the Hib conjugate. There is hope that this conjugate will do similar kinds of herd immunity effects, but we don't have any information, other than the promise that there may be a herd immunity effect. So that's one issue that I think we need to make sure that's at least raised with the manufacturers as this vaccine moves forward.

Second issue is memory - does memory protect? I don't whether memory protects or not. That's a big question in the meningococcal world about whether memory is going to protect, whether it's simply -- waning of antibody, as Dr. Farley points out, is going to be a real issue. And whether memory response, whether it may be a laboratory phenomena, but is that memory response going to protect for meningococcal disease?

There is some data, as we've mentioned this morning in the U.K. suggesting that at least in toddlers who were getting a different immunization schedule, that even though they generate these memory

responses, they don't protect after one year, so that's of concern with these conjugate vaccines. So I think the whole issue of memory and whether it's going to be protective or not, and whether a boosting response is going to protect is another important area for this particular vaccine. Is it going to be better than the currently available polysaccharide, and those are important questions from a public health standpoint, anyway, that need to be considered as this vaccine moves forward.

DR. OVERTURF: Dr. Royal.

DR. ROYAL: I concur with all of the points made by Dr. Stephens, and I'd like to sort of just get something out of my head and ask whether one might have expected to see some change in the response to Menomune merely by instead of administering subcutaneously, to give it IM.

DR. OVERTURF: Does the sponsor want to address that question? Dr. Frasch.

DR. FRASCH: If you look at the very early trials in the early 1970s, which Dr. Gotschlich and colleagues were involved with, and at that time they

did not know whether they were going to give the vaccine subcu or IM. And limited studies were done at that time, and there was no difference in the immune response to the vaccine given IM versus subcu. The only difference was some differences in adverse reactions, but not immunogenicity.

DR. OVERTURF: Are there any other comments on discussion Point Three? Dr. Gellin.

DR. GELLIN: I mean, just to round it out, given that the age range is 11 to 55, we have identified a number of populations that would have different vaccines given concomitantly, adolescents, laboratorians potentially, international travelers. I would throw the military on that list, as well, and I don't know if there's any here can speak to that, but knowing it's a vaccine that's probably of interest to them, that's probably another set of studies given the databases they have that looks at vaccine safety.

DR. OVERTURF: Dr. Karron.

DR. KARRON: And just to amplify on Dr. Gellin's comment, we actually saw data in the aggregate presented from age 11 to 55. I think as

there are post-licensure studies done, it would be interesting to see some breakdown by age regardless of the issue of concomitant vaccines administered to see if responses are equivalent across the age range.

DR. OVERTURF: Are there other comments? I'd like to then go ahead and proceed to question number four; which is, please identify any issues - I think we've partly begun to address this - that should be addressed in post-licensure studies. Are there any additional issues that haven't been addressed? I think in addition to breaking things down by - we've already mentioned host, and age, probably racial and ethnic backgrounds need to be looked at more closely also. Dr. Whitley.

DR. WHITLEY: I think the qualifier on that, and Barbara and I were just talking about it a minute ago, is that not only under-represented minorities, but the populations that may not best be served by current nutritional balances in the United States, where you would you expect a less advantageous an immune response, and I wouldn't make that comment just for this vaccine, but for vaccine development in

general.

DR. OVERTURF: Yes, Dr. Farley.

DR. FARLEY: I think that obviously the post-marketing surveillance is important, but I think general surveillance for meningococcal disease and the distribution, ongoing activities of surveillance where we look for so-called replacement, or shifting towards predominance of B disease, for instance, serogroup B disease because it's not in the vaccine, obviously following that. I think it would be very interesting to look at carriage studies, depending on what the recommendations actually are, whether it's going to be a solid block of the population that it will be recommended for, and whether you can look at that age group for reduction in carriage of the vaccine serogroups.

DR. OVERTURF: Yes, Dr. Stephens.

DR. STEPHENS: Just to echo what Dr. Farley was saying, I think the U.K. really had a very aggressive program as they went forward with their conjugate vaccine to look at issues of carriage, and to look at issues of serotype or serogroup

replacement. And those studies are still ongoing, and still very helpful. And I think similar kinds of studies really need to be done in this country to look at the effects of this conjugate. Again, it depends to some degree on how it's introduced, and how it's used, but those were very important studies in understanding how that vaccine in that country was and is working.

DR. OVERTURF: Just to echo some of the previous comments, actually those of Dr. Stephens, I think the issue about how -- whether this is a better vaccine really is going to be a very early critical issue, because many assumptions are being made about this vaccine, and I'm not sure that the data yet is completely adequate to suggest that. I think it's going to be difficult for practitioners and providers to make a decision a little bit about which one of these vaccines they want to use. So I think that will be an early immediate issue, mostly because many of the issues that we've talked about which leave big blank spaces in the knowledge about this vaccine. Dr. Self.

DR. SELF: So if that distinction hinges, at least in part, on herd immunity or secondary transmission, I guess I would make a plug for considering study designs to directly measure the differences in secondary transmission rather than relying on some of the presumed surrogates that I've heard thrown out since I think probably none of those are validated in any reasonable way for rates of secondary transmission.

DR. OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: Yes. I'd like to echo what Dr. Farley said, because this idea of the serogroup changing to stay one step ahead of the vaccine has actually been noted in the very earliest studies. If you look at the oft quoted studies of Artenstein, and then they were re-analyzed actually by Lee Sabbath about 30 years ago, where they actually looked at the numbers and they found that, indeed, there was this shift from the serotype you were protected against, and now there was more of a different serotype, so this is actually a very real thing that's been known about for quite a long time,

and would be well worth looking at in the post-marketing surveillance.

DR. OVERTURF: Dr. Karron.

DR. KARRON: This is really a question for the FDA, and it has to do with issues of lot variability. And my question is really what will routinely be done to look at issues of lot variability. The data that we saw today, there were some values that fell outside of the bounds. They were not considered to be biologically significant, but I'd like to know what is routinely done.

DR. FRASCH: Well, this is addressed actually in two aspects. One, we do routine lot release of every batch that the company makes. And two, we do yearly inspection of the company, and checking the batch records for the vaccine. And we also periodically go over the company, their specifications for the vaccine, not only does it meet the specification, but is there any drift within the specifications. And so we try to keep up with the company, and with our own records to see if there's any change in the physical/chemical characteristics of

the product.

We have the problems of looking at the vaccine physical chemically, but then at the same time we know that there's a lot of variation in different populations, so a single studies is sometimes somewhat difficult to know if that's really a variability in the vaccine, or a variability across the population. But the important point is that we do do routine lot release of every batch of the vaccine, and we follow the specifications.

DR. KARRON: So that lot release testing is both physical chemical characterization and immunologic characterization?

DR. FRASCH: No, no. It's only physical chemical characterization. No, there's no requirement for a vaccine to be tested - I would guess you mean in the clinic. No, there's no requirement like that. That's for any vaccine.

DR. OVERTURF: Dr. Stephens.

DR. STEPHENS: This is another comment concerning one component of this vaccine, and that's the A component. We don't A disease to any great

degree in this country, but this is the first A conjugate really to come to approval, and in some parts of the world, sub-Sharan Africa, for example, the A conjugate could make a huge difference in terms of burden of disease. I would like to encourage them to - and I think they are - to think about that particular issue in terms of the use of this vaccine in populations where A disease is much more prevalent. And to get more information about the A component of this vaccine for that particular purpose.

DR. OVERTURF: Are there other comments?

DR. DENSEN: In addition to Dr. Farley's comments, I'd like to add what may be an obvious comment; which is, that I think it would be very important to do the surveillance for vaccine failures, particularly in some of the subgroups such as the complement-deficient patients or splenectomized patients, because I think the possibility is there that there will be a potentially higher failure rate in those populations - that would be number one.

And I guess I feel, David Stephens and others, that while I agree very strongly with the

comments about serogroup analysis and carriage rates and whatnot, and that the efficacy of the vaccine has not been demonstrated per se, I think on the other hand there are no data to suggest that the opposite is true. And I think I would not personally like to come away from this session with the idea that I'm feeling negative about the opportunity, the potential, because I think the potential is very great based on the other conjugate vaccines that have been used.

DR. OVERTURF: Any other questions, discussion? We were supposed to take a break at 3:30, but I'm going to ask the members of the FDA if there's any other issues that we have not addressed for today's session before I call for an adjournment. Then I think the meeting for the day is adjourned. We re-adjourn at 9 a.m. tomorrow morning.

(Whereupon, the proceedings in the above-entitled matter went off the record at 3:05 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/CBER

Date: September 22, 2004

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.