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UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

100th MEETING

WEDNESDAY,
SEPTEMBER 22, 2004

The Advisory Committee met at 10:00 a.m. in the Versailles Ballroom of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Gary D. Overturf, Chair, presiding.

PRESENT:

GARY D. OVERTURF, M.D.	Chair
PETER DENSEN, M.D.	Temporary Voting Member
MONICA M. FARLEY, M.D.	Member
BRUCE GELLIN, M.D., M.P.H.	Temporary Voting Member
RUTH A. KARRON, M.D.	Member
DAVID M. MARKOVITZ, M.D.	Member
PAMELA McINNES, D.D.S.	Temporary Voting Member
STEPHEN PETTEWAY, Jr., Ph.D.	Acting Industry Representative
CINDY LYN PROVINCE, R.N., M.S.N.	Consumer Representative
WALTER ROYAL III, M.D.	Member
STEVEN SELF, Ph.D.	Member
DAVID STEPHENS, M.D.	Temporary Voting Member
RICHARD WHITLEY, M.D.	Member
BONNIE M. WORD, M.D.	Member
CHRISTINE WALSH, R.N.	Executive Secretary

FDA REPRESENTATIVES:

CARL FRASCH, Ph.D.
LUCIA H. LEE, M.D.
KAREN MIDTHUN, M.D.

SPONSOR REPRESENTATIVES:

GARY CHIKAMI, M.D.
MICHAEL D. DECKER, M.D.
GREG GILMET, M.D., M.P.H.
LUC KUYKENS, M.D., M.P.H.

C O N T E N T S

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

10:00 a.m.

CHAIRMAN OVERTURF: Good morning. I'm Gary Overturf, the Chair of the VRBPAC. And I'd like to call the meeting to order. This is the 100th meeting of VRBPAC so it's a momentous occasion.

I'd like to turn the meeting now over to Christine Walsh who has the requisite announcements.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome you all to the 100th meeting of this Advisory Committee.

Today's session will consist of presentations that are open to the public. We did not hold a closed session today as described in the Federal Register notice of September 3, 2004. Tomorrow's meeting will consist of both open and closed sessions.

I will ask that during our meeting all committee members identify themselves each time they

speak. We have a transcriber present who will need your assistance in order to accurately transcribe all comments to the appropriate committee member.

I would now like to read into the public record the conflict of interest statement for today's meeting.

The following announcement addresses conflict of interest issues associated with the Vaccines and Related Biological Products Advisory Committee Meeting on September 22 and 23, 2004.

The Director of the Center of Biologics Evaluation and Research has appointed Drs. Peter Densen, Bruce Gellin, Pamela McInnes, and David Stephens as temporary voting members for this meeting.

To determine if any conflicts of interest existed, the Agency reviewed the submitted agenda and all relevant financial interests reported by the meeting participants.

As a result of this review, and based on the FDA Draft Guidance on disclosure of conflict of interest for special government employees participating in an FDA product-specific Advisory

Committee meeting, the following disclosures are being made.

Dr. David Stephens has been granted a waiver under 21 U.S.C. 355(n)(4) of Section 505 of the Food and Drug Administration Modernization Act for unrelated royalties of less than 5,001 dollar per year from a competing firm.

Dr. Stephens may participate fully in the discussion of the safety and efficacy of Menactra and the Phase III Thai Trial for the prevention of HIV-1 infection.

We would like to note for the record that Dr. Stephen Petteway is the Acting Non-Voting Industry Representative for this committee representing regulated industry. Dr. Petteway's appointment is not subject to 18 U.S.C. 208. He is employed by Bayer and thus has a financial interest in his employer.

Dr. Peter Palese recused himself from this meeting.

Also Dr. Steven Self recused himself from the discussion on September 23 regarding the Phase III Thai Trial for the prevention of HIV-1 infection. He

is participating fully in the discussion on September 22nd regarding the safety and efficacy of Menactra manufactured by Aventis.

Members and consultants are aware of the need to exclude themselves from the discussions involving specific products or firms for which they have not been screened for conflict of interest. Their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose products you wish to comment upon. Waivers are available by written request under the Freedom of Information Act.

That ends the reading of the conflict of interest statement.

Dr. Overturf, I turn the meeting back over to you.

CHAIRMAN OVERTURF: Again I'd like to welcome the members to the Vaccines and Related Biological Products Advisory Committee and all those in the audience and members of the FDA staff.

At this time I'd like the members to introduce themselves and we will begin with Dr. Markovitz. And I would ask that you introduce yourself and who you represent.

MEMBER MARKOVITZ: Yes, I'm David Markovitz. I'm a Professor of Medicine in Infectious Diseases at University of Michigan in Ann Arbor.

MEMBER ROYAL: Walter Royal. I'm an Associate Professor of Medicine at Morehouse School of Medicine in Atlanta, Georgia.

MEMBER FARLEY: I'm Monica Farley. I'm a Professor of Medicine, Infectious Diseases, at Emory University in Atlanta.

MEMBER McINNES: Pamela McInnes, Deputy Director of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases.

MS. PROVINCE: I'm Cindy Province. I'm the Associate Director of the St. Louis Center for Bioethics and Culture and I'm the Consumer Representative.

MEMBER GELLIN: I'm Bruce Gellin. I'm the

Director of the National Vaccine Program Office at the Department of Health and Human Services.

CHAIRMAN OVERTURF: I'm Gary Overturf. I'm a Professor of Pediatrics and Pathology and Director of Pediatric Infectious Disease at the University of New Mexico in Albuquerque.

MEMBER STEPHENS: I'm David Stephens, Professor of Medicine, head of the Division of Infectious Diseases at Emory University in Atlanta.

DR. PETTEWAY: I'm Steve Petteway. I'm Vice President for Preclinical R&D and Pathogen Safety for Bayer Health Care.

MEMBER WORD: I'm Bonnie Word. I'm Assistant Professor of Pediatrics at Baylor College of Medicine, Texas Children's Hospital.

MEMBER WHITLEY: Rich Whitley, University of Alabama at Birmingham, Professor of Pediatrics, Microbiology, Medicine, and Neurosurgery.

MEMBER DENSEN: I'm Peter Densen. I'm a Professor of Internal Medicine and Infectious Diseases at the University of Iowa where I'm also the Executive Associate Dean.

MEMBER SELF: Steve Self, Professor of Biostatistics at the University of Washington in Seattle.

MEMBER KARRON: Ruth Karron, Associate Professor of International Health and Pediatrics, Johns Hopkins University.

CHAIRMAN OVERTURF: Thank you.

At this time we'll begin the introduction to the license application. I'll ask Dr. Carl Frasch to take the podium.

DR. FRASCH: Okay. What I would like to do is introduce the license application, give some basic background information about the license, and provide some historical and regulatory context in which this application is being presented today.

The vaccine is meningococcal (groups A, C, Y, W135) polysaccharide diphtheria toxoid conjugate vaccine and the trade name is Menactra.

The application was received on December 17th, 2003 as an electronic BLA. And this is the first meningococcal conjugate vaccine submitted for licensure in the U.S.A. and the first electronic BLA

we've handled in my office.

And the proposed indication is active immunization of adolescents and adults, 11 to 55 years of age, for prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W135.

The vaccine is formulated to contain per 0.5 microgram dose, four micrograms of each of the four meningococcal polysaccharides conjugated to approximately 48 micrograms of diphtheria toxoid. The vaccine contains no adjuvant.

Now for approval of a new vaccine, it must be shown to be both safe and effective. Concerning the effectiveness requirement, I cite a relevant regulatory standard and I quote:

"Proof of effectiveness shall consist of controlled clinical investigations as defined in 314.126. Unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product and that an alternative method of investigation is adequate to substantial effectiveness, alternate methods such as serological response evaluation in clinical studies

and other laboratory evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists."

And I will present more information on the serological response evaluation aspect.

First, non-inferiority designs are used to evaluate efficacy indirectly when placebo-controlled efficacy designs are not feasible. Thus, non-inferiority assessments are in reality indirect efficacy evaluations.

So you need to know that there is an existing polysaccharide vaccine made by the same manufacturer. The brand name is Menomune and the age indication is the same as for Menactra. And thus the licensing strategy taken by Aventis Pasteur was to show that Menactra was not inferior to Menomune in terms of immunogenicity and safety.

Now I want to show that the use of immunogenicity has been used previously. Thus, the licensing strategy to show that Menactra is not inferior to Menomune in terms of immunogenicity and

safety has been used for the approval of Haemophilus polysaccharide-based vaccines and, as I will show shortly, meningococcal vaccines.

First in December 1987, we approved Haemophilus b conjugate vaccine, then called PRP-D, for the same indication as a previously approved polysaccharide vaccine based on immunogenicity.

Then in March of 1993, we approved the third Haemophilus b conjugate vaccine called PRP-T, again based on immunogenicity data.

Now regarding the use of immunological correlates, in September of 1999, CBER presented in front of the VRBPAC a presentation, Use of Immunologic Surrogates for Demonstration of Protective Efficacy of Meningococcal Conjugate Vaccines.

In brief, the committee concluded that immunological correlates can be used to demonstrate protective efficacy of meningococcal conjugate vaccines for those two years of age and older.

Now they did not specifically define what they meant by immunological correlates. So, therefore, I'm going to present some more information

relating to that aspect.

During the IND process, CBER and Aventis Pasteur agreed upon the path to be taken to demonstrate the effectiveness of Menactra. This path was based upon historical perspective.

First, how the meningococcal polysaccharide vaccine was licensed, the current meningococcal polysaccharide vaccine, and two, what is known about immunological correlates of protection for meningococcal disease.

Looking first at the meningococcal polysaccharide vaccines in the mid-1970s, we licensed meningococcal group A, group C, and the A/C polysaccharide vaccines, all based on clinical efficacy trials.

Then in 1981, we approved the current four-valent or quadrivalent meningococcal polysaccharide vaccine Menomune. This approval was based upon immunological criteria. We asked that greater than fourfold rise in the serum bactericidal activity be present in 90 percent of adults three to four weeks after immunization.

Now looking at the efficacy trials for the group C polysaccharide vaccine, these were done in U.S. Army recruits and you can see at the bottom right corner that the protection was approximately 90 percent.

Now looking at the group A polysaccharide vaccine, since group A meningococcal disease occurs primarily in Africa, most of these studies were done in Africa except for two done in Finland. Again, in the bottom righthand corner, we see that the efficacy was 97 percent for the group A polysaccharide vaccine.

Now based on the efficacy studies and other clinical data, the critical role of bactericidal antibodies in protection against meningococcal disease has been demonstrated.

First, studies in the U.S. Army recruits in the 1960s showed a direct correlation between susceptibility to meningococcal disease and absence of serum bactericidal antibodies.

Second, the highest incidence of meningococcal disease occurs in infants between six and twelve months of age. They have the lowest

bactericidal antibody concentrations at this age.

Third, individuals deficient in serum complement components C5, C6, C7, or C8, the membrane attack complex, have markedly increased susceptibility to systemic meningococcal disease. And have repeated meningococcal infections. Thus bactericidal antibody is a surrogate for protective immunity.

And I will show illustrations of the first two points on this slide now.

First, we see that the peak incidence of disease occurs in children under two years of age at the time when they have the lowest levels of serum bactericidal antibodies. This is taken from the classic studies by Goldschneider and Gotschlich published in 1969.

Now the second illustration is taken from their same publication, and this is an actual table from their publication, and since it's rather complicated, I've summarized the data in the following slide.

They had the unique opportunity to collect serum on recruits at the point when they entered into

training. They collected serum on 492 recruits at Fort Dix in 1968. They found that 438 had bactericidal antibody in their blood at the time they started training. And there was no disease in this population.

Fifty-four of the 492 initially lacked bactericidal antibodies. So let's look at those 54 individuals. Twenty-four became exposed to the group C epidemic strain, 11 developed bactericidal antibody, no disease.

The other 13 failed to develop bactericidal antibody. There were five confirmed group C meningococcal cases in this population for an attack rate of 38 percent. There was a sixth suspected case which would have brought the attack rate to 46 percent in this one population that was initially bactericidal negative.

Now you will see today data presented using human complement on one hand and rabbit complement on the other. These studies that I've just shown you used a human serum bactericidal assay using intrinsic complement as the source, the sera were

diluted one to four, and they looked at either was it bactericidal or was it not. And this correlated with protection or susceptibility.

Then at the time of the approval of the first polysaccharide vaccines, the WHO, in cooperation with then the Bureau of Biologics, developed a standardized bactericidal assay based on using baby rabbit sera.

This specified that the sera would be taken immediately prior and two to four weeks after immunization. Baby rabbit serum was to used as the complement source. The titer would be the reciprocal of the dilution with greater than 50 percent killing and the titers of the sera from at least 90 percent of subjects should show a fourfold or greater rise after immunization indicating that they have responded to the vaccine.

Thus, based upon the historical record, the primary immunogenicity endpoint for Menactra is determination of percent of vaccinees having a fourfold or greater rise in bactericidal antibody for Menactra compared to the licensed vaccine Menomune

using baby rabbit serum as the complement source.

So to conclude, as part of the review process, CBER investigators conducted a pre-license inspection of Aventis Pasteur manufacturing facility in Swiftwater, Pennsylvania. And I should say that the inspectional findings were satisfactory.

And so today, the focus of the presentations are going to be first -- the CBER presentations, first Dr. Lucia Lee will provide the CBER clinical review of safety and efficacy and introduce the questions that will be directed to the committee.

And second, after lunch, I will present two questions for the committee to vote upon and an additional two items for discussion and comment.

Thank you.

CHAIRMAN OVERTURF: Are there any questions of clarification?

(No response.)

CHAIRMAN OVERTURF: If not, we'll proceed now with the presentation by the sponsor in support of Menactra.

DR. KUYKENS: Mr. Chairman, members of the Advisory Committee, ladies and gentlemen, FDA staff, good morning. My name is Luc Kuykens. I've Vice President of Regulatory Affairs for Aventis Pasteur.

Aventis Pasteur is pleased today to have the opportunity to present Menactra, our meningococcal quadrivalent conjugate vaccine to you.

Please note that during the development of this vaccine, we also used the abbreviation of TetraMen D, a name you may have seen in some of your briefing documents.

The outline of the sponsor's presentation today is as follows:

Following my introduction, Dr. Gilmet will review the epidemiology of meningococcal disease and the importance of meningococcal conjugate vaccines for public health.

Dr. Michael Decker will review the immunogenicity profile of our product.

And Dr. Gary Chikami will review the safety data.

While the currently available quadrivalent

meningococcal polysaccharide vaccine, Menomune, has been demonstrated to be efficacious and is recommended for use in high-risk groups in outbreak situations, there is a definite public health need for an improved meningococcal vaccine.

Such vaccine should provide persistent bactericidal antibodies, ability to prime and boost, lack hyporesponsiveness, reduce carriage, and provide herd immunity. Menactra has the potential to meet these needs.

As mentioned by Dr. Frasch, Menactra consists of four polysaccharides, A, C, Y, and W135. Four micrograms of each polysaccharides is covalently linked to 12 micrograms of diphtheria toxoid for a total of 48 micrograms of diphtheria toxoid. Note that Menomune contains 50 micrograms of each polysaccharide.

Menactra is adjuvant and preservative free. It's presented in a liquid formulation for intramuscular administration.

Both the polysaccharides and the diphtheria toxoid are currently licensed as part of

Menomune and Tripedia respectively.

The clinical experience was gained with Menactra includes more than 10,000 participants, over 7,600 adolescents and adults and 2,600 children.

However, the indication requested in the BLA submission, which is the subject of this application, is for the prevention of invasive meningococcal disease in adolescents and adults from 11 to 55 years of age for which the clinical database is over 7,600.

The objective of our clinical program was to demonstrate non-inferiority to the standard of care, our widely-used polysaccharide vaccine Menomune, for both safety and immunogenicity.

In addition, we started the concomitant administration of Menactra with Td and Typhim Vi vaccines.

The data to be presented today will show that we met all pre-specified criteria for non-inferiority and that's both for safety and immunogenicity.

In addition, Dr. Decker will review some

important new data that recently became available in a follow-up study, a three-year follow-up study to one of our pivotal trials indicating that Menactra has the characteristics expected from a conjugate vaccine: antibody persistence, immune priming and boosting, and lack of hyporesponsiveness.

I would like you to note that these data were not part of the initial BLA and have not been reviewed by the FDA. However, in discussions with the FDA, they have agreed for us to share these data with you today.

Thank you and I would like to introduce Dr. Gilmet now who will review the epidemiology of meningococcal disease.

DR. GILMET: Thank you, Luc.

I appreciate the opportunity to present the epidemiology of meningococcal disease to the VRBPAC Committee this morning.

Historically, the epidemiologic situation in the U.S. first drove Aventis Pasteur to begin the development of Menactra over a decade ago.

In this presentation, I will summarize the

following topics: the unique clinical challenge of meningococcal disease, the current epidemiological situation in the U.S., recent European and U.K. epidemiology, benefits of conjugate vaccines when compared to polysaccharide vaccines, data from the recent C conjugate mass vaccination campaign in the U.K., and conclude the presentation with summary statements.

Meningococcal disease presents a number of unique clinical challenges. *Neisseria meningitidis* is the most common cause of bacterial meningitis in children, adolescents, and young adults. The meningococcus is able to cause disease outbreaks and epidemics.

The meningococcal sera group distribution continually changes over time and has wide geographic variability. Meningococcal disease often strikes young, otherwise healthy individuals. And yet the overall mortality rate has remained in the 10 to 15 percent range for decades despite better understanding of the disease and improved treatment modalities.

It's estimated that 60 percent of patients

with meningococcal disease experience symptoms for less than 24 hours before finally presenting to the hospital for care.

Lastly, the disease can be difficult to diagnose, has tremendous emotional impact, and causes disproportionate fear and alarm. Collectively these factors argue for a vaccine-based primary prevention strategy.

Our initial Menactra application will be for 11 to 55 year olds. The epidemiology I'm about to show will provide additional evidence to support the public health need for a quadrivalent meningococcal conjugate vaccine in this target age group.

Let's first look at current U.S. epidemiology. Now unlike most of the world, meningococcal disease is caused by multiple sera groups in the U.S. and their relative proportions constantly shift over time. Serogroup Y, for example, increased from nine to 28 percent in the past decade.

About one-third of disease is caused by serogroup B for which no licensed vaccine is currently available in the U.S. However, approximately two-

thirds is caused by the vaccine-preventable serogroups C, Y, and W135.

You'll note that serogroup A disease is very rare in the United States although it was responsible for epidemics as recently as World War II. And it remains a concern for travelers to hyperendemic or epidemic areas such as sub-Saharan Africa.

Meningococcal disease is also cyclical with the peak endemic incidence as high as 3,500 cases annually. You'll note on this slide that currently we're at a low point in the cycle, however it is anticipated this will change in the near term based on historical trends.

Shown here are recent incidence data from CDC national surveillance. Note that the highest absolute incidence occurs in infants in whom serogroup B is the dominant cause. However, the next most important group is adolescents and young adults represented by a wide incidence peak.

The high percent of vaccine-preventable cases in adolescents and young adults relative to younger age groups is demonstrated on this slide. For

clarity, the non-vaccine-preventable cases caused by serogroup B have been grayed out. The serogroup C, Y, and W135, potentially vaccine-preventable cases, are represented in various colors.

It's important to note here that the percentage of adolescent and young adult cases that are potentially preventable with a quadrivalent vaccine is in the 70 percent range. In addition, this CDC Vital Statistics data broken down by age group shows that adolescents and young adults also have the highest number of deaths due to invasive meningococcal disease.

This slide shows data from Lee Harrison's Maryland study of risk factors and outcomes and is further evidence of lethality in adolescents and young adults. Note that 15 to 24 year olds are several times more likely to die if they acquire meningococcal disease than those less than 15 years of age.

Also, the percentage of vaccine-preventable disease in this Maryland sample is significantly higher in the 15- to 24-year-old group and exceeds 80 percent.

Now historically, the Army was the first to implement the mass vaccination program in military recruits and did so with great success beginning in 1971. Here you can see the progression for monovalent to bivalent and finally quadrivalent polysaccharide vaccines.

In this highly controlled setting, a dramatic reduction in both the number of hospitalizations as indicated by the blue bars and rate of hospitalizations, indicated by the solid purple line, was observed.

College students are another group where meningococcal vaccination is a consideration. Like Army recruits, they share a common risk factor such as age and close contact with their peers.

Not surprisingly then, college freshman, dormitory residents, and to an even greater degree college freshmen living in dormitories, have relative risks several times higher than either all 18 to 23 year olds or all college students highlighting the need for routine vaccination coverage in this population.

We'll next look at recent epidemiologic data from the U.K. and Europe. Unlike the situation in the U.S., approximately 95 percent of disease in the U.K. and Europe is caused by serogroup C and B. Note also the relative absence of serogroup Y in Europe.

Although only one-third of the disease burden in Europe is vaccine preventable, namely that caused by serogroup C, the decision, nonetheless, was made in the U.K. to pursue a mass vaccination program in adolescents, the group with the highest age-specific mortality rate.

Data from this U.K. study shows that acquisition of meningococcus increases very rapidly when you put young people in close contact.

Carriage rates approach 25 percent four days after college matriculation and up to 35 percent one to two months later. This contrasts with carriage rates in the overall population that are typically reported to be 10 percent in the literature.

Next I'll summarize important differences between polysaccharide and conjugate vaccines.

Polysaccharide vaccines have several limitations when compared to the newer conjugate vaccines. Most important, conjugate but not polysaccharide vaccines, elicit a T-cell-dependent immune response.

And as a consequence of this T-cell activation, only conjugate vaccines induce long-term memory, persistence of protection, and booster responses. These, in turn, lead to a reduction in bacterial carriage and resultant herd immunity.

Finally, conjugate vaccines do not result in hyporesponsiveness or immune tolerance after repeat vaccine doses. These are a well-described phenomenon with polysaccharide vaccines. Taken together, it's evident that conjugate vaccines confer important immunologic enhancements.

I'll now address a recent U.K. experience with C conjugate meningococcal vaccines. Because of the observed benefits of conjugate vaccines we just looked at, the U.K. launched a mass vaccination program with monovalent serogroup C conjugate vaccine.

The high risk 15 to 17 year old age cohort was initially targeted. And over the ensuing year,

the program was expanded to include younger age groups. And because the program was so successful, other European countries, Canada, and Australia soon followed suit.

The impressive U.K. results are highlighted on this and the next four slides. The baseline data before the program was initiated in November 1999 shows a steady upward trend in cumulative cases.

During the first year of program implementation, serogroup C disease was nearly halved. After year two, serogroup C disease is almost entirely eliminated.

This slide shows serogroup C disease reduction percentages by age group. And they range from 64 to a high of 89 percent. Overall disease reduction was 81 percent in the U.K. program.

Likewise, the important outcome of carriage reduction for serogroup C when comparing pre- and post-program rates was 66 percent in adolescents with no significant change observed in the other serogroups.

And as a result of that reduction in carriage, there was a dramatic herd immunity effect and reduction in attack rates of 48 to 80 percent in the unvaccinated. This also parallels the experience seen with the earlier introduction of both Hib and pneumococcal conjugate vaccines.

Now traditionally, the existing vaccine standard has been the licensed A, C, Y, W135 polysaccharide vaccine Menomune. Menomune is indicated for travelers, individuals with potential occupational exposure to meningococcus, household or institutional contacts of cases, college students living in dormitories, immune-compromised individuals, and military recruits.

Menomune is highly effective, has been available for over 20 years, has an excellent safety profile, and is widely used. However, polysaccharide vaccines such as Menomune have limitations a conjugate vaccine such as Menactra will overcome.

The expected benefits of Menactra, if given as part of a universal vaccination program of 11 to 18 year olds in the U.S., include the following: a

persistence of protective antibody, an ability to both prime and boost, and a lack of hyporesponsiveness after a booster dose.

Now in a few minutes, Dr. Decker will show you important data that demonstrate these immunologic attributes of Menactra. In addition, we expect to see upon further study and experience a reduction in carriage and resultant herd immunity with Menactra.

And finally, the potential exists to replicate the U.K. findings in the U.S. and broaden the coverage to include serogroups A, Y, and W135.

Historically, we are approaching a very exciting and important milestone in public health. Over the past several decades, conjugate vaccines have substantially impacted both Hib and pneumococcal disease. The last of the triad of major causes of bacterial meningitis in children, adolescents, and young adults is the meningococcus.

We now have a quadrivalent conjugate vaccine that should greatly impact the meningococcal disease burden in the United States.

In summary, the key epidemiologic findings

are the following. Meningococcal disease is a serious and challenging public health problem. Adolescents and young adults are at high risk. The U.K. program demonstrated the ability to reduce carriage, induce herd immunity, and eradicate serogroup C disease.

Menactra should prevent meningococcal disease by as much as 70 percent in U.S. adolescents if used as part of a universal immunization program targeting 11 to 18 year olds.

Thank you for your attention. I'd now like to introduce Dr. Michael Decker who will present the Menactra immunogenicity data.

DR. DECKER: Thanks, Greg.

I'm Dr. Michael Decker. And I will present to you the immunogenicity data in support of our application for licensure of Menactra.

First, I'll discuss the basis for licensure, which is the non-inferiority of Menactra as compared to Menomune.

Second, I'll talk about how we measure immunogenicity.

Third, I'll provide an overview of the

clinical trials and then show you the results of the comparative clinical trials in adolescents followed by the results of the comparative clinical trials in adults.

And then I'll close with a review of the results of studies of the concomitant administration of Menactra with other vaccines.

First, a brief word on the non-inferiority approach. Non-inferiority studies are particularly suitable when a standard of care exists such as Menomune.

In order to conduct the comparative evaluation of the candidate product versus the standard of care, it is necessary to define a threshold, a non-inferiority margin.

Even two exactly equal products will not return exactly the same results in two populations under study. These sample results will have some difference.

And the non-inferiority criteria place a bound on the uncertainly concerning this comparison so that one then knows that if shown non-inferior, the

candidate product is a suitable alternative. And as I said, the evaluation of Menactra involves demonstrating its non-inferiority with respect to Menomune.

There are a number of ways to measure immunogenicity. And in the clinical laboratory, the most common measurements involve assays that measure the quantity of antibody present such as ELISAs or RIAs and produce results that typically are measured in milligrams or micrograms per ml.

And although useful, these assays tell us nothing about the performance of the antibody that is being measured, only its quantity.

Other assays called functional assays actually tell us about the performance of the antibody but typically these are more burdensome to conduct and are not generally available in clinical laboratories. These include assays such as CHO cell assays, serum bactericidal assays, and so on.

Now as Dr. Frasch mentioned, some 35 years ago, Gotschlich, Goldschneider, and colleagues conducted a seminal study at Fort Dix, New Jersey.

They drew serum samples from about 15,000 Army recruits arriving at Fort Dix for basic training. And then followed them for about eight weeks to observe the occurrence of invasive meningococcal disease.

Over that period of time, 54 cases occurred. They analyzed the sera from those 54 persons as well as 10 control samples for each case.

And what they found was that there was an extraordinarily high predictive value of having serum bactericidal assay titers of one to four or greater in your serum. Having that amount of SBA conferred 98.4 percent protection from invasive meningococcal disease.

They also showed that this protective property could be absorbed from the serum by group-specific polysaccharides demonstrating the specificity of this association.

And as Dr. Frasch mentioned, in 1999, VRBPAC considered these issues and endorsed the use of serologic data, immunogenicity data, in support of the licensure of specifically conjugate meningococcal vaccines for those indications where a polysaccharide

is licensed.

We will present to you serum bactericidal assay results. This is the standard approach for meningococcal assays. The results are directly relevant to protection from the disease.

It was the basis for licensure not only of Menomune several decades ago but also in the U.K. for the licensure of their currently used conjugate C vaccines.

Our assay conforms to CDC and WHO standards and we participated in the Inter-Laboratory Collaborative Study. Our assays fully validated.

Now when one measures immunogenicity, there are a variety of endpoints that could be looked at. We'll present to you several different analyses.

First we'll look at fourfold rises which are defined as the proportion of those participants whose post-immunization titers are at least four times their pre-immunization titers.

This was specifically the basis for Menomune licensure and for licensure of the vaccines in the U.K. And it's the primary non-inferiority

outcome measure in all of the core clinical trials that I'll be presenting to you.

I'll also show you geometric mean titer results, the normalized average of the post-immunization titers. And this measure was a co-primary outcome in some of the core clinical trials and in the remainder, it's a descriptive measure.

We also calculated seroconversion rates, which represents the proportion of those who were initially seronegative, defined as less than 1:8, who then have a fourfold or greater rise. These analyses are descriptive and for the interest of time, I won't show them to you in the slides today but they are in your handouts.

And finally, I'll show you some reverse cumulative distribution curves, which provide a graphical depiction of the overall distribution of antibody in the population participating. And these, again, are descriptive.

We have a number of clinical trials to present to you.

MTA02 is the primary comparative trial

between Menactra and Menomune in adolescents.

MTA19 is a recently completed follow-up study in a subset of that same population who were given Menactra again three years later.

MTA04 is a safety comparison in adolescents. I'll not be presenting to you results from that study but my colleague, Dr. Chikami, will.

MTA09 is the analogous trial to MTA02 but in adults. It's the primary comparative trial between Menactra and Menomune in those 18 to 55 years of age.

MTA14 is the lot consistency trial also conducted in adults.

MTA12 is a study of the concomitant administration of Menactra and Td vaccine conducted in adolescents.

And MTA11 is a study of the concomitant administration of Menactra and Typhim VI typhoid vaccine conducted in adults.

In the aggregate, these clinical trials enrolled 7,642 persons to receive Menactra and 3,041 persons to receive Menomune, for a total of over 10,000, nearly 11,000 participants in the clinical

trials.

The gender distribution of those receiving Menactra and the racial ethnic distribution is shown on this slide.

As you see, for the adolescents there was an approximately even balance between males and females whereas for adults, there was approximately a two to one ratio of females to males. And in each case, those distributions reflect the patient populations of the clinics and centers that participated in the clinical trials.

Overall 86.2 percent of the participants were white, non-Hispanic. And 14 percent were other than white, non-Hispanic.

MTA02 is the first study that I'd like to show you. This was a multicenter, randomized, comparative clinical trial in U.S. adolescents; 881 healthy 11 to 18 year olds participated, approximately half of whom received Menactra and half Menomune.

The hypothesis was that the short-term immune response of Menactra was not inferior to that of Menomune. And I emphasize here short term for two

reasons. First, that is what we measured. We looked at the antibody responses 28 days after immunization.

But secondly, the short-term aspect is important to consider because polysaccharide vaccines, including Menactra, raise excellent antibody responses in full grown persons in the short term.

The deficiencies of polysaccharide vaccines lie in the durability of their responses, their inability to prime, and the fact that they are not very effective in very young persons.

I'll show you a number of slides that look like this. This one shows you the fourfold rises. Others will show you similar data. For each of these, the four serogroups are rated across the slide.

For each serogroup Menactra is compared to Menomune, Menactra will always be in the powder blue and Menomune in the pale yellow. And below each of the bars, you find the data that support those bars.

In this case, these are the fourfold rises among adolescents given Menactra or Menomune by serogroup. And what you see is a very close correlation between the responses for the Menactra and

the Menomune recipients. And so not surprisingly, all the non-inferiority criteria were met.

Now I'll also show you a number of slides that look this. In each case, there's a vertical dash line or perhaps two vertical dash lines indicating the bounds of the non-inferiority margin that was defined.

Within, or hopefully within those bounds, one will find the results of the four serogroups or whatever else the comparison might be, a little vertical line and a number indicating the point estimate, and the 95 percent confidence interval.

If the entire 95 percent confidence interval lies within the non-inferiority margin, then the criteria for non-inferiority have been met. If any part falls outside, then for that comparison, the criteria were not met. And as you see here, all the non-inferiority criteria were met for fourfold rises among adolescents.

This slide shows you the geometric mean titers from that same study. For groups C, Y, and W, you see again a close correlation between the Menactra and the Menomune geometric mean titers whereas for

serogroup A, it appears that the Menactra group has substantially higher geometric mean titers than the Menomune group.

This is a reverse cumulative distribution curve. Along the X axis are arrayed in ascending order various antibody titers. Along the Y axis are the percentages of the overall population who achieved any given titer.

So for the very lowest titer, four, the percentage is 100 percent. And as the titer value rises, the proportion of the population that achieved that level or greater declines.

Now on this slide, there are four lines drawn. The two that are the pale pastels here are the pre-titers for Menactra and Menomune respectively. And the bolder pastels are the post-immunization, the 28-day titers for Menactra and Menomune.

This is serogroup A, which was the serogroup that you saw in the prior slide where the Menactra and the Menomune results looked different. And one of the virtues of a reverse cumulative distribution curve is it enables you to understand the

sources of difference.

In this case, what you see is that the two vaccines appear identical up to this point here, titer of 256 or 512. And then they start to diverge with the Menactra value superior, particularly in this range of titers from 4,000 through 32,000 or 64,000.

And from this I conclude that although the geometric mean titers for Menactra were substantially higher than those for Menomune, the two vaccines actually are identical in the range that is predictive of protection from disease.

The human complement value 1:4 that was identified by Gotschlich and Goldschneider in their study 35 years ago, has been viewed to be equivalent to a titer of 1:128 by baby rabbit complement based on studies conducted both on laboratory validation studies and on studies out of the U.K. looking at their experience with their vaccine program.

And as you see, both vaccines are achieving 100 percent coverage at 1:128 and even above that. The difference lies in these high titers.

So from that, I conclude that the

difference in GMTs that was shown on the prior slide for A is probably of no clinical importance with respect to the performance of these two vaccines in the population.

Here are the RCD curves for serogroup C, for serogroup Y, and for serogroup W135.

Next I'd like to show you the results from study MTA19. MTA19, which was recently completed and was not part of the submission to the FDA, enrolled a subset of participants in MTA02 and then offered them Menactra immunization.

Seventy-six persons from MTA02 who received Menactra, 77 who had received Menomune, and an additional 88 persons enrolled at this point in time for this study who had never received any prior meningococcal vaccine participated in MTA19. All received one dose of Menactra.

And the objectives of our study were first to evaluate the persistence of antibody over the three-year interval from the initial vaccination MTA02 to the time of this second vaccination in MTA19.

Secondly, to evaluate the ability of

Menactra to prime and to boost.

And third, to evaluate the response of Menomune recipients to a subsequent dose of Menactra.

Now the inset slide here looks very much like the GMT, the geometric mean titer slide that I showed you a few moments ago for MTA02. Indeed it differs only in that this version of the slide contains only those persons who went on to participate in MTA19.

So it therefore provides the proper backdrop for this graph which shows you the level of antibody that these persons had three years after this point in time. So if you compare these bar pairs to these bar pairs, what you see is substantially better persistence of the antibody in the Menactra than in the Menomune recipients.

And indeed, although the study was not powered to achieved statistical significance for these comparisons, two of these four comparisons are statistically significant and the other two are borderline.

Now recall we also enrolled at the time of

MTA19 a vaccine-naive population to provide a further comparison. These in coral here are shown the antibody levels of persons of the same age who have never received vaccine. And so the difference between the Menactra vaccinated, the Menomune vaccinated, and the naive, I think, is clear.

These reverse cumulative distribution curves further demonstrate the antibody levels prior to re-immunization. These are the antibody levels three years after Menactra, three years after Menomune, or in a naive population that's never been vaccinated.

These are the curves for serogroup A, for serogroup C, for serogroup Y, and for serogroup W135.

Now on this particular scale, the pre-titers prior to re-vaccination look very similar here although you've just seen that they are not, in fact, similar. Upon administration of Menactra, those who had previously received Menactra had a rapid and very high increase in their antibody levels.

In the case of serogroup C here, up to about 18,000 within eight days following re-

immunization.

The naive population not previously vaccinated also had an excellent antibody response to Menactra but substantially lower than that of those who were previously primed, thus demonstrating the benefit of prior Menactra administration and the fact that Menactra does prime the immune system.

Here are the results for serogroup Y, for the Menactra-primed, and for the naive.

The results from serogroup W135 for the Menactra-primed and the naive.

And the results of serogroup A for the Menactra-primed and the naive. In this case, the naive responded equally well to the Menactra-primed, probably reflecting the fact that most of the population is already pre-primed for serogroup A due to cross-reacting antibodies.

Then the last question we wanted to evaluate was what happens when you give Menactra to a person previously immunized with Menomune?

Now this was the initial Menomune pre-titer and the antibody response after initial Menomune

administration. This is the antibody level of this group three years later.

The literature tells us pretty clearly that if given Menomune at this point, because of the phenomenon of hyporesponsiveness associated with polysaccharide vaccine re-administration, the post-re-administration antibody level would be expected to be in this range down here and would not be expected to reach the level seen previously.

What we found was that when this population was given Menactra, here you see it for serogroup C, there was an antibody response that exceeded that that would have been expected.

Here you see serogroup A, serogroup Y, and serogroup W135.

So from these repeat administration study data, we conclude that Menactra is associated with superior persistence of antibody. At three years, the Menactra SBA geometric mean titers are higher than seen following Menomune or in naive controls. And you see that clearly in the RCD curves also.

We believe this study demonstrates the

ability of Menactra to prime and to boost because we see a rapid, high anamnestic response that far exceeds the response of naive controls for all serogroups except A where they are equal.

And we see the prior Menomune recipients who were given Menactra demonstrate a rapid increase in bactericidal antibody to levels that exceed those that would be expected were they re-immunized with Menomune.

And we conclude, therefore, the Menactra demonstrates the important immunological characteristics that are expected of a conjugate vaccine.

Now I'd like to turn to results in adults.

MTA09 is the primary comparative trial in adults; 2,554 healthy U.S. adults 18 to 55 years of age of whom approximately 60 percent received Menactra and 40 percent received Menomune. And, again, the hypothesis was that the short-term immune response of Menactra is not inferior to that of Menomune.

We begin again with the fourfold rises. And you see, again, close correlation between the

Menactra and the Menomune responses for all four serogroups. And the non-inferiority criteria are met.

Here are the geometric mean titers, reasonably close correlation, less so for serogroups Y and W135, however, take note that even the lowest geometric mean titer is well over a 1,000. All the non-inferiority criteria were met.

And here are the reverse cumulative distribution curves. For serogroup C and A, the curves closely compare. For serogroups Y and W135, the curves diverge here as we saw earlier when we looked at the MTA02 study.

And once again, as in that study, the two vaccines appear to perform identically up to a titer of well over the 128 benchmark for clinical protection. Probably up to 256, it appears they are identical. And the real divergence in the curves is in the range of titers above a 1,000, from 2,000 or 4,000 up to 16,000 or so.

So we conclude again that although the GMTs differ, this difference probably has no relevance to clinical protection from disease.

MTA14 was the lot consistency trial conducted in adults. Approximately 2,000 healthy U.S. 18 to 55 year olds participated. Three-quarters of these received Menactra, one-quarter respectively to each of three consistency lots of Menactra. And the remaining quarter of the participants receive Menomune.

The hypothesis was that the three Menactra lot geometric mean titers would be equivalent as reflected by a maximum ratio between any two GMTs of 1.5.

Here are those geometric mean titers by serogroup, by lot. You see some variation amongst the three. In this particular case, there is no titer lower than 2,000. So all of these anti-responses are very high.

There are 12 non-inferiority comparisons to be made of which nine passed and three failed. For the three failures, their point estimates are contained within the bounds but one end of the 95 percent confidence interval crosses the boundaries. And as noted in the FDA briefing document, all of

these confidence intervals are fully contained within a 2.0 ratio.

Here are the geometric mean titers for serogroup A, C, Y, and let me pause here. You note again the same thing we've seen before, that up to a titer well above the putative protective level, the two vaccines -- I mean in this case the three lots perform virtually identically.

And it's only for the titers that are well above 1,000 that we see any differences. So although these three did not meet the consistency criteria for the GMTs, slightly exceeding the margin, we believe that difference is of no clinical relevance.

And serogroup W135.

Here is another view of the results of this lot consistency trial. In this table, you see the various lots by serogroup and the GMTs that you've just seen graphically. But also shown are the percent achieving a fourfold rise and the proportion who had titers of 128 or greater.

Now what you see is that there is substantially less variation in the percent achieving

fourfold rise and virtually no variation, no more than plus or minus one percent, in the proportion achieving a titer of 128 or greater.

Now I'd like to turn to the studies of concomitant administration of Menactra with another vaccine.

First, we looked at the co-administration of Menactra and Td vaccine in adolescents. We enrolled approximately 1,000 healthy adolescents to receive either Menactra and Td simultaneously or Td and placebo initially followed by Menactra 28 days later.

And we looked at this question because it seemed likely to us that if licensed, Menactra might be given concomitantly with Td since the first Td booster for adolescents is recommended at about the same age that Menactra might well be given.

The hypothesis was that the concomitant administration of the two vaccines would not be inferior in any way to the sequential administration of the two vaccines.

Here you see the fourfold rises in SBA

titer by serogroup. Now the colors have changed because the vaccines represented are different. The green bars represent Menactra plus the concomitant vaccine, in this case Td. And the pale yellow bar here is Menactra alone 28 days after Td.

So the question is are the green bars non-inferior to the yellow bars? I think you see graphically that they are. And indeed the statistical analysis demonstrates their non-inferiority.

You saw there that the results 28 days later tended to be a little lower than the results with concomitant administration, which might raise in your minds the question of well, perhaps concomitant is okay but there's some problem with sequential administration.

So to lay that question to rest, I've put on this slide the results from MTA02, which was the primary comparative trial in the same age group. And what you see is that for three of the four serogroups, the sequential administration and the primary comparative trial Menactra results are essentially identical. And for the fourth serogroup, they are

superior.

So from this we conclude that neither the sequential nor the simultaneous administration of Menactra and Td in any way interferes with Menactra antibody responses.

Now with respect to the tetanus and diphtheria antibody responses, I need to show you a slide that is structured a little bit differently because antibody levels to tetanus and diphtheria can vary widely in the population and persons who already have very high antibody levels are much less likely to achieve a fourfold rise upon re-vaccination.

So by agreement with FDA, we analyzed these data by separating the population into those who had very high pre-titers, in this case to tetanus, which is the blue group, and were held to the standard of requiring a twofold rise and person who did not have very high pre-titers, which is the group shown in green, for which we calculated fourfold rise percentages. And then the pale yellow bar shows the aggregate information.

Now the first block of three bars is the

Menactra and Td group. And the second block of three is the person who received only Td along with placebo. And the question is how each bar compares to its companion color bar in the other group.

And what you see here clearly is that there's no difference at all. So that administering Menactra with Td and administering Td alone produce identical proportions of fourfold or twofold response and identical overall results.

For the diphtheria antibody levels, the results are similar. They differ only in that the proportion achieving a twofold response is greater in the concomitant administration than in the Td alone group.

And for both tetanus and diphtheria, all pre-specified non-inferiority criteria were met.

Finally, I'd like to show you the results of trial MTA11, which was a study of the concomitant administration of Menactra and Typhim Vi typhoid vaccine in adults.

We looked at this because it occurred to us that many adults who receive Menactra might be

travelers or military or others who would be simultaneously receiving a travel vaccine such as Typhim Vi.

We enrolled in this study 945 healthy adults of whom approximately half received Typhim Vi and Menactra simultaneously and half receive Typhim Vi and placebo initially with Menactra given a month later.

And the hypothesis again was that the concomitant administration of these two vaccines would not produce results that were inferior to the sequential administration.

Here you see the geometric mean titers at Day 28 following either receipt of Menactra and Typhim Vi together or Menactra 28 days after Typhim Vi. Once again, the results are very similar for the two groups.

Here are the fourfold rises in SBA titer by serogroup. And the results, again, are very similar or if different, the concomitant administration group is a little bit higher than the sequential administration group.

All non-inferiority criteria were met.

As far as the response to the Typhim Vi vaccine, we analyzed these data by looking at the proportion in which either titered greater than 1.0, a Typhim titer. Here's the proportion for the concomitant administration group. And here's the proportion for the sequential. And clearly the concomitant is not inferior to the sequential as supported by this statistical analysis.

So based on all these data, we conclude that Menactra is consistently immunogenic in adults and adolescents and satisfied all non-inferiority criteria.

Menactra serum bactericidal antibody levels three years after administration are superior to those seen following Menomune or in naive controls. One dose of Menactra primes from memory as demonstrated by a rapid and very high booster response upon re-immunization.

Menactra offers a superior re-immunization pathway for prior Menomune recipients.

And finally, Menactra demonstrates the

important immunologic characteristics that are expected from a conjugate vaccine.

At this time, I'd like to ask Dr. Gary Chikami to present to you the safety results from our studies.

DR. CHIKAMI: Thank you, Michael.

The overall results from these studies demonstrate that Menactra was safe and well tolerated among adolescents and adults. All the pre-specified safety criteria were met. And the safety profile of Menactra is consistent with what would be expected from a diphtheria toxoid conjugate vaccine.

The clinical safety program was designed to meet the requirements for regulatory approval and to establish the clinical impact of the overall safety profile for the product.

The main objectives were one, to compare the safety profile of Menactra to the safety profile of Menomune. The primary objective was to demonstrate that the rate of severe systemic reactions was similar between Menactra and Menomune recipients. The comparison was based on severe systemic reactions

because these were felt to be the most clinically significant.

It's important to note that the local reactogenicity profile was expected to be different between Menactra, a protein conjugate vaccine containing diphtheria toxoid, and Menomune, a polysaccharide vaccine.

The second major objective was to characterize the overall safety profile of the product. The following safety data were collected: immediate reactions were collected for the 30 minutes post-vaccination.

Solicited and systemic local reactions were selected because they are clinically significant to the characterization of the overall safety profile of Menactra. These lists were developed with input from the FDA Review Division.

Unsolicited reactions were collected during two time periods. All adverse events were collected from Day Zero through Day 28. From Day 29 through Month 6 in studies which included a six-month follow up, any adverse event that included a new onset

of a sign, symptom, laboratory abnormality that promoted medical intervention were collected.

And finally, serious adverse events were collected throughout the entire follow-up period for each study.

The overall rates for immediate reactions were similar across the vaccine groups; .3 percent Menactra recipients and .2 percent of Menomune recipients reported an immediate reaction.

We looked more closely at the eight cases that were coded as syncope in the Menactra recipients. We found that five of the eight cases were described as vasovagal reactions, two were described as syncope in one as a syncopal episode.

None were reported as a serious adverse event, and none required medical intervention, and all were covered on the same day without sequelae. Based on these descriptions, we conclude that there are no significant concerns regarding these cases.

The categories of events included in the list of systemic reactions was based on experience with Menomune and other conjugate vaccines.

A pre-established list of medical conditions was defined that meet study protocol. The clinical severity of the reported events were documented as mild, moderate, or severe according to a defined rating scale.

Information was collected on participant diary cards from Day Zero through Day Seven. The presence or absence of an event and the intensity of the event were collected on a daily basis. This allowed us to determine the duration of the event as well as the duration of the most intense portion of any reported event.

The safety comparison objective was to demonstrate that Menactra was non-inferior compared to Menomune with regard to participants who reported a serious systemic adverse event.

For MTA04 and MTA09, the criteria for non-inferiority was based on the ratio of the 95 percent confidence interval of subjects presenting at least one severe systemic reaction. The upper limit of the 95 percent confidence interval was set at three.

For MTA02 and MTA14, the criteria for non-

inferiority was based on the 95 confidence interval of the difference in the percentage of subjects reporting at least one severe systemic reaction. In this case, the upper limit of the confidence interval was set at 10 percent.

The difference in the non-inferiority criteria used across the two groups of studies were the result of ongoing discussions with the Review Division.

For MTA02 and MTA14, in addition to the criteria specified in the protocol, we applied the stricter criteria used in MTA04 and MTA09 and those are the results that I'll present to you this morning.

For solicited systemic reactions in the studies in adults, all of the non-inferiority criteria were met.

MTA04 was a comparative study in adolescents and a total of 3,235 participants were evaluated for safety. Ninety-nine percent of the participants completed the six-month follow up.

The frequency of any systemic reaction was 55 percent in the Menactra group and 48.7 in the

Menomune group. The rates for severe solicited systemic reactions were 4.3 percent and 2.6 percent in the Menactra and Menomune groups respectively.

In the assessment of the primary safety endpoint, the ratio of the percentage of participants with any severe solicited systemic reaction is 1.66. And the upper bound of the 95 percent confidence interval is 2.56, meeting the criteria for non-inferiority.

While the upper bound of the confidence interval does fall within the specified criteria for non-inferiority, there was a higher rate of reactions on the Menomune subjects in this one study.

For each of the solicited systemic reactions, we assessed frequency, intensity, and duration. The most common systemic reactions reported were headache, fatigue, malaise, and arthralgia. Most events were classified as mild. The median duration for any solicited systemic event was three days in the Menactra group and two days in the Menomune group.

With regard to severe reactions, the rates for headache, fatigue, malaise, and diarrhea were

higher in the Menactra recipients. As I'll show you in subsequent slides, those same events were not significantly higher in Menactra recipients in the other comparative studies. And none of these reactions were reported as severe adverse reactions.

There were no other significant differences between the rates of severe events between the two groups. And for events that were reported as severe, the duration of the severe component was one day.

MTA02 was the second comparative immunogenicity and safety study in adolescents; 880 participants were evaluated for safety and 98.9 percent completed the study.

The rates for any solicited systemic reaction were 57.2 percent in the Menactra recipients, 51.9 percent in Menomune recipients. And for severe reactions, 3.9 percent and 4.1 percent in the Menactra and Menomune recipients respectively.

The ratio of the percentage of participants with any severe solicited systemic reaction is .95 and the upper limit of the confidence

interval is 1.82, again meeting the criteria for non-inferiority.

In this study, the most common systemic reactions were headache, fatigue, anorexia, and diarrhea. Again, most events were classified as mild. Overall, the median duration for the solicited systemic events was three days in both vaccine groups.

In contrast to MTA04, the other study in adolescents, there were no significant differences in the rates for any of the severe systemic reactions for the Menactra and Menomune recipients. The median duration for the severe component of these events was one day.

The rate of systemic reactions observed in MTA12 provide a useful context for the rates that I've shown you in MTA04 and MTA02. In MTA12, Menactra was given concomitantly with or 28 days after Td vaccine in healthy adolescents, a population similar to MTA04 and MTA02.

In this study, the rates of systemic reactions were similar in the groups that received Td concomitantly with Menactra or Td with placebo. The

rates of systemic reactions observed in MTA04 and MTA02 were similar to those observed in MTA12 for Td vaccine.

Overall the rates in the adult studies were comparable to the results seen in the adolescent studies and the non-inferiority criteria for each study were met.

MTA09 was a comparative study in healthy adults and a total of 2,530 participants were evaluated for safety. Ninety-four percent completed the six-month follow up. The rates of any solicited systemic reaction was 61.9 percent in the Menactra recipients and 60.3 percent in the Menomune recipients.

The rates for severe systemic reactions were 3.8 percent and 2.6 percent in the Menactra and Menomune recipients respectively.

The ratio of percentage of participants with any severe solicited systemic reaction was 1.47. And the upper limit of the confidence interval is 2.28, meeting the criteria for non-inferiority.

The most commonly reported systemic

reactions were headache, fatigue, malaise, and arthralgia. And the rates were similar across the vaccine groups.

Most systemic reactions were classified as mild and the median duration was three days in both groups.

Except for chills, which were higher in the Menactra recipients, there were no significant differences in the rates of any of the severe systemic reactions reported in the Menomune and Menactra recipients.

In MTA14, comparative safety was evaluated in Menactra and Menomune recipients in a total of 1,140 adults. Ninety-four percent completed the six-month follow up. The rates of any solicited systemic reaction was 53.4 percent compared to 49.2 percent.

And in this study, the rate of severe systemic reactions were lower in the Menactra recipients at 2.2 percent versus 5.5 percent in the Menomune group.

The ratio in the percentage of participants with any severe solicited systemic

reaction was .4. And the upper limit of the confidence interval .75, meeting the criteria for non-inferiority.

The most commonly reported systemic reactions were headache, fatigue, malaise, and arthralgia. Again, most systemic reactions were classified as mild and the median duration of the reactions was three days in both vaccine groups.

Except for malaise, which in this case was reported higher in the Menomune group as compared to the Menactra group, there were no significant differences between the rates of any of the severe systemic reactions reported.

To put the rates of systemic reactions in the two adult studies in context, this slide shows the results from MTA11. In this study, Menactra was given either concomitantly with or 28 days after Typhim Vi vaccine in healthy adults, populations similar to those enrolled in MTA09 and MTA14.

The rates for solicited systemic reactions reported in MTA09 and MTA14 were in the same range as those seen with Typhim Vi whether given concomitantly

with Menactra or with placebo.

It was anticipated that the local reactogenicity profile of Menactra, a protein conjugate vaccine containing diphtheria toxoid, would be different from Menomune, a polysaccharide vaccine. While this was observed in the clinical studies, data from the concomitant use studies with Td and Typhim Vi vaccine show that the local reactogenicity profile of Menactra was similar to that for these other licensed vaccines.

Solicited local reactions were defined in the protocol for each study and included redness, swelling, induration, and pain at the injection site. Information was recorded on participant diary cards on Day Zero through Day Seven.

Clinical intensity was documented as mild, moderate, or severe according to predefined rating scales. For induration, swelling, and redness reported as severe, the measurements of the actual event were to be recorded.

In the adolescent studies, local reactions were higher in the Menactra recipients as compared to

the Menomune recipients. Pain at the injection site was the most frequent local reaction reported and were reported in the ranges shown on this slide.

While the rates of injection site pain were higher in the Menactra recipients as compared to the Menomune recipients, the observed rates were similar to those or lower than the rates observed for Td vaccine in MTA12.

For all groups, the majority of pain was reported as mild. The median duration of pain was two days in the Menactra recipients compared to one day in the Menomune recipients and one to two days in the Td recipients.

Severe pain was uncommon and was reported in 0 to .8 percent of Menactra recipients and .2 percent of the Td recipients. The median duration of the severe component was one day.

As with pain at the injection site, the reported rates of induration, swelling, and redness were higher in the Menactra recipients compared to the Menomune recipients. The rates in the Menactra recipients were in the same range as those reported by

Td recipients in MTA12.

The majority of the events were mild in intensity for all vaccine groups and the median duration was one day in the Menomune recipients, one to two days in the Menactra and Td recipients. Severe induration, swelling, and redness were uncommon.

Overall, these rates show while the rates of local reactions were higher in the Menactra recipients as compared to Menomune recipients, the local reactogenicity profile of Menomune is comparable to that of Td.

Within MTA12, the overall rates for local reactions observed at the Menactra injection sites, the two bars in the center of the graph, were lower than those observed at the Td injection sites, the two bars on the extreme left of the graph.

While the overall local reaction rates observed in MTA02 at 72.4 percent and MTA04, at 62.7 percent, were higher than those observed at the Menactra injection sites in MTA12, they were similar to or lower than the rates observed at the Td injection sites.

Similar to the studies in adolescents, the rates of local reactions were higher in Menactra recipients compared to Menomune recipients in the adult studies. Pain at the injection site was the most frequent local reaction and was more frequently reported among Menactra recipients compared to Menomune recipients. The rates of pain among Menactra recipients was less than those observed in Typhim Vi recipients in MTA11.

Most injection site pain was reported as mild and the overall median duration of pain was two days.

Severe pain was reported in 0 to 1.8 percent of Menactra recipients compared to 0 to .1 percent of Menomune recipients and .4 to .8 percent of Typhim Vi recipients. The duration of severe pain was one and one-half to two days for the Menactra recipients compared to one day for Menomune recipients and two and one-half days for Typhim Vi recipients.

Again, the rates of induration, swelling, and redness were higher in the Menactra recipients compared to Menomune recipients however these rates

were lower than those observed at the Typhim Vi injection sites in MTA11.

The majority of the events were mild in intensity and the median duration was one to two days in Menomune recipients, two days in Menactra recipients, and one day in the Typhim Vi recipients. Severe induration, swelling, and redness were uncommon.

The overall results from these studies in adults show that while the rates of local reactions for Menactra were higher compared to Menomune, these rates were lower than observed for Typhim Vi vaccine.

Within MTA11, the rates of local reactions reported at the Menactra injection sites, the two center bars, were lower than those reported at the Typhim Vi injection sites, the two bars on the extreme left of the graph.

The local reaction rates reported in MTA09 and MTA14 were in the same range as those rates reported for Menactra injection sites in MTA11. But again, these rates were lower than those reported at the Typhim Vi injection sites.

Unsolicited adverse events and serious adverse events were reported at similar rates across the two vaccine groups in the clinical studies. This table shows the most frequent unsolicited adverse events that occurred in at least one percent of participants. And there were no differences in the nature of frequencies of events across the two vaccine groups.

We found similar results for the six-month follow-up period in studies that included that follow up.

A total of 5.8 percent and 5.7 percent of Menomune recipients reported at least one unsolicited adverse event. There were no differences between the nature or frequency of these events. None of the events was considered either probably or definitely related to study vaccine by the investigators.

And there was no apparent increase in the frequency of new-onset asthma, diabetes mellitus, or autoimmune disease.

With regard to SAEs, there were 77 participants in the Menactra group who reported a

serious adverse event and 39 among the Menomune recipients. All except one were categorized as unrelated to study vaccine by the investigator.

Across the six studies, there were two deaths reported in study participants. Both were in study MTA14, one a motor vehicle accident occurring 109 days after study vaccination in the Menactra group, the other a drug overdose occurring 79 days after vaccination in the Menactra group. Both were classified as unrelated to study vaccine by the investigators.

Overall, the safety data from the clinical trials demonstrate that Menactra was safe and well tolerated among adolescents and adults. Menactra met all agreed non-inferiority criteria with respect to safety.

Specifically Menactra was demonstrated non-inferior to Menomune with respect to the proportion of subjects reporting at least one severe systemic reaction.

While the rates of local reactions seen with Menactra are higher than those reported with

Menomune, they are comparable or less than the rates seen with Td vaccine and are consistent with expectations for a protein conjugate vaccine.

And Menactra may be administered either concomitantly with or one month after Td vaccine or Typhim Vi vaccine.

Thank you. And I'll turn the podium back to Dr. Kuykens.

DR. KUYKENS: Thank you, Gary.

Let me know briefly present the conclusions of the sponsor.

In our immunogenicity presentation we have shown data indicating that Menactra is highly immunogenic both in adults and adolescents, that Menactra's immune response is non-inferior to Menomune's, our widely-licensed polysaccharide vaccine, and that Menactra can be administered concomitantly with Td and Typhim Vi vaccines.

Dr. Decker reviewed important recent data from a three-year follow-up study to our pivotal MTA02 trial indicating that Menactra has the characteristics expected from a conjugate vaccine, antibody

persistence, immune priming and boosting, and lack of hyporesponsiveness.

Dr. Chikami presented the safety data indicating Menactra is safe and well tolerated, has a non-inferior safety profile in regards to severe systemic reactions compared to Menomune, and a local reactogenicity profile similar to Td vaccine.

Menactra can be administered concomitantly with Td and Typhim Vi vaccines.

In conclusion, from a risk/benefit point of view, the local reactogenicity rates for Menactra were as expected for a diphtheria-containing conjugate vaccine, somewhat higher than those of Menomune. But were similar to those seen with Td vaccine.

The benefits shows for Menactra include the excellent immunogenicity profile in both populations of adults and adolescents, the improved antibody persistence versus the polysaccharide vaccine, the priming and boosting capabilities, and the lack of hyporesponsiveness.

This concludes the presentation of the sponsor and the presenters will be happy to take any

clarifying questions at this point.

CHAIRMAN OVERTURF: Thank you. I'd like to thank Drs. Kuykens, Gilmet, Decker, and Chikami for the presentation. And I open the floor for any questions or clarifications.

MEMBER MARKOVITZ: Yes, David Markovitz, University of Michigan. I have a question probably for Dr. Decker. Michael, do I understand correctly that when Menomune priming data are strictly historical? You don't have a direct comparison?

DR. DECKER: No, we did not enroll a group in that study to receive Menomune again. That would have raised ethical questions because the literature, I think, are really very -- pretty uniform on the hyporesponsiveness.

For example, I'm reminded of Dr. Granoff's study because I'm looking right at him. And in his study he found no improvement in antibody whatsoever from baseline upon re-administration of Menomune. Now that's probably the most pessimistic study out there. Others have shown some improvement in antibody.

But I think we already know that if you re-administer Menomune, you're happy to see any increase in antibodies compared to the prior value. You really get your benefit out of a polysaccharide vaccine with the first administration.

MEMBER MARKOVITZ: Okay, thanks.

CHAIRMAN OVERTURF: Yes, Dr. Karron?

MEMBER KARRON: Two questions. The first is really a follow on to that question. And it's that although clearly the people who got Menomune and then Menactra had much higher antibody responses than you'd expect with two doses of Menomune, if I'm reading the data correctly, all of the antibody titers were lower than in people who only received placebo.

And that was particularly true with group C where I think the placebo recipients had titers of about 2,000 whereas the people who got Menomune and then Menactra had titers of about 500.

And my question is do you think that Menomune is blunting the response to Menactra?

DR. DECKER: Well, let me clarify for a moment. No one received placebo. There was --

MEMBER KARRON: I'm sorry. I misspoke. So people in that study who received a first dose of Menactra compared to people who received Menomune followed by Menactra.

DR. DECKER: Yes, I saw what you did that those who had previously received -- those who were naive --

MEMBER KARRON: Yes.

DR. DECKER: -- and received Menactra had superior antibody responses apparently than those who were previously vaccinated with Menomune and then received Menactra.

Although I think that's probably a correct observation, I think it's not the key question because those people in the U.S. population who previously received Menomune received it for good reason and they cannot go back and become vaccine naive.

And the real public health question is what's the best thing to do for them if they again or continue to need protection from invasive meningococcal disease. And heretofore we've had only the limited choice of do nothing or received the

polysaccharide again.

And I hope that we'll now have the better choice of receive the conjugate.

MEMBER KARRON: My second question actually just had to do with a choice of Typhim Vi as the representative traveler's vaccine. I was wondering what considerations lead you to chose that particular vaccine.

DR. DECKER: I can't help but note that we make it.

(Laughter.)

DR. DECKER: And I wonder if that influenced the choice. But I would have to defer to my colleagues to know more precisely.

DR. KARRON: Okay.

CHAIRMAN OVERTURF: Dr. Whitley?

MEMBER WHITLEY: Rich Whitley, University of Alabama. This is a simple question. If I read your data correctly, you only followed those patients 28 days in the prime/boost experiment. Do you have any later data, six months, one year, two years? Or the data are not there yet?

DR. DECKER: You're referring to immunogenicity data?

MEMBER WHITLEY: Yes, yes.

DR. DECKER: We have data from the studies that we have conducted in children, age range toddler through ten. And we anticipate presenting those data to FDA in support of a license extension once Menactra is licensed for the 11 to 55.

And because the question that you raise is of the most acute interest in that population, it's in those populations that we followed six month antibody levels. And we could show you those data if you like.

CHAIRMAN OVERTURF: Dr. Stephens?

MEMBER STEPHENS: Two questions about MTA19. One has to do with the serogroup C data. And it looked like in comparison to W135, and in Y, and even A that there was a significant greater fall off of C. And, in fact, a number of those individuals were at what I would consider borderline SBA titers at three years.

Can you comment on that particular data? That's the first. It's 66, I think, in the slide.

DR. DECKER: Slide on please. I believe this is the slide you're referring to?

MEMBER STEPHENS: Right. I mean just in comparison to the other antibody data, if you look at the other reverse cumulative distribution curves, this is the greater fall off at three years.

And the question really had to do with some of the, you know, the recent C data in the U.K. that is of some concern. And just your comments about was this greater than you had anticipated in terms of the fall off in C antibody with Menactra.

DR. DECKER: I don't think it was greater than was anticipated because what we've seen from data from other countries that have been previously immunizing with C is that C does tend to fall off.

What you see here is a uniformity -- let me rephrase that -- the only comparison we have internally here is the comparison, of course, between the Menactra recipients, the Menomune recipients, and the naives.

And the relative comparisons between those three groups across the four serogroups tells a fairly

consistent story. Now it can be a complicated story because the four serogroups really behave somewhat differently. A and C co-circulate in the United States at relatively high rates. And, therefore, what we see, particularly in more modern sera, is that baseline rates tend to be a little bit higher for those.

I'm sorry, I said A and C. I mean Y and C co-circulate. A has cross-reacting antigens in the environment that can raise antibody levels. And so W is really the only one that's, as far as we know, not stimulated by circulating, cross-reacting antigens. And isn't stimulated by fairly high levels of circulating organisms.

And because of this, for many of these pre-titers or post-titers when you look across the four serogroups, you see different patterns. So we already know that.

Within that context, what we're seeing here for C was not surprising. I think it's consistent with the global data.

MEMBER STEPHENS: The second question has

to do with boosting of A. Do you really think that you saw boosting of A?

DR. DECKER: Are you referring to in MTA19?

MEMBER STEPHENS: Yes.

DR. DECKER: Could we go back to the core slide for MTA19? Yes, this is the one.

Now by the classic definition that I have applied when I showed the first slide, you would say there's no boosting because the naive did equally well. But I think we have to take --

MEMBER STEPHENS: And I guess the polysaccharide alone does about the same?

DR. DECKER: No, there's no polysaccharide -- I'm sorry, yes, I misspoke and I apologize. The polysaccharide alone did about the same.

But A is unique. Pre-titers for A are much higher because of the cross-reacting antigens. Now if you look at the population distribution of existing antibodies in the non-vaccinated for A versus the other serogroups, you see much, much higher levels.

For example, 60 to 80 percent of the population will have levels that are of 64 or 128. And so the way we interpret this result that you're looking at is that the naive controls for A are not really naive. They are essentially pre-primed. That's our best understanding of what's being seen here. And so they're getting, in fact, what's an anamnestic response to the polysaccharide.

Now for the other three serogroups that don't have the cross-reacting antigens such as the *E. coli* and the bacillus that circulate, we didn't see that.

CHAIRMAN OVERTURF: Dr. Self?

MEMBER SELF: Yes, I have a few questions just to help connect the dots from the protective effects and the relationship with SBA that were in the Fort Dix study and the measurements that were used in these studies that some actually show the non-inferiority of these two vaccines.

The piece of data that I don't see here is in a reference which, I admit, I didn't see. And that is a paper that shows the correlation between the

assays using human complement and the baby rabbit complement.

Do you have that data or could you explain what this one liner is that says that one titer for one assay correlates with a different titer for the other assay?

DR. DECKER: There are several lines of evidence that support that. And if I could see Slide IM68 please?

Dr. Luis Jodar who wrote on behalf of WHO in this publication summarized the available data which supported WHO's assertion that 1:128 provided a conservative comparison to the 1:4 in humans. And there were three key points.

First, that SBA baby rabbit titers less than 1:8 appear to correlate closely with human complement titers less than 1:4. In other words, that category might be predictive of potential susceptibility.

SBA baby rabbit titers that were greater than 1:128 correlated well, in fact were even more strongly predictive of protection than human

complement titers of greater than 1:4. And baby rabbit titers that fall between those two measures, between 1:8 and 1:32 were of uncertain predictive value.

In other words, they couldn't establish a tight correlation either with protection or with non-protection. So with baby rabbit, there is a gray zone between 8 and 128. Below 8 seems to correlate with below 1:4 by human. And above 128 seems even more predictive of protection in 1:4 in humans.

MEMBER SELF: So by correlation with the baby rabbit titers greater than 128, does that mean that a baby rabbit titer of over 128 will predict with very high, you know, with what specificity a human titer over 1:4?

DR. DECKER: If you'll permit -- let me phrase that just a hair differently and then I can agree.

A baby rabbit titer of 1:128 or greater is believed to be as highly predictive of protection from invasive meningococcal disease as is a human complement titer of 1:4 or greater.

MEMBER SELF: Based on the Fort Dix data?

DR. DECKER: No, based on -- well the 1:4 number comes out of Fort Dix and similar studies.

MEMBER SELF: Right.

DR. DECKER: The 1:128 number comes flows out of two sources, laboratory correlation studies just looking at the assays themselves but more importantly correlations of antibody levels in human populations and the protection of those human populations from disease.

MEMBER SELF: In vaccine studies or natural history studies?

DR. DECKER: Well, in both. Data coming out of the U.K. looking at, for example, data -- in the deployment of their vaccination program, the British looked at many of these parameters and they published a number of papers.

And they looked, for example, at antibody levels in persons who had been immunized and found what levels correlated with protection.

MEMBER SELF: Is that data in the package that you submitted? Because that would seem to be

rather key, directly showing that the measurement that you're using in your studies is related at an individual level to risk in human populations.

DR. DECKER: I don't know if those references are included in the briefing document or not. Part of the context for us was that it was -- the use of baby rabbit as the basis for evaluation of both vaccines was predefined with the Agency. And so we approached from that starting point.

But recognizing that this is a question of interest, I familiarized myself with the data so I could answer your question.

MEMBER SELF: Okay. So a second part of this question really has to do whether the relationships that are cited here between antibody titers and protection are consistent across the various serogroups that are being identified as potentially being protected against by this vaccine.

I could see only subtype serogroup C in the references that were given here.

DR. DECKER: Most of the modern data relate directly to serogroup C because the vaccines,

the conjugate vaccines that are now deployed in population-based programs are C only vaccines. Menactra will be the world's first multivalent conjugate meningococcal vaccine.

The use of serogroup A protective vaccines in Africa, of course, happens. But those are not broad-based population programs such as you see in the U.K. and in the other countries that have adopted the conjugate meningo vaccines.

Rather they are delimited interventions aimed at aborting epidemics and they don't give rise to the same level of data.

MEMBER SELF: So there isn't data comparable say to the Fort Dix data for the other serogroups really?

DR. DECKER: There is not the same body of data for the other serogroups. There are no data that contradict the assumption that what's true for C is true for the others. But neither is there the same wealth of data for the others that there is for C.

MEMBER SELF: And just one last follow up. Is there, for the other subgroups then, data

comparable to the one that's -- Jodar looking at the relationship between the two assays?

DR. DECKER: Yes, there are data. And we have some very limited data in that regard. If I could go to Slide IM69 please?

One of the things that the Agency asked us to do was to use a small subset of serum from MTA02 which was the core comparative trial in adolescents.

Slide on please, I'm sorry.

I believe this was MTA02. I could be mistaken it was MTA09. But that's not an important point. What this slide compares is two standards, the licensure -- the basis for licensure for Menomune originally, of the conjugate C vaccines in the U.K. and now of Menactra, the primary non-inferior comparison is the proportion achieving a fourfold rise.

The standard of comparison that was established 35 years ago by Goldschneider and colleagues was a 1:4 by human complement. So a reasonable question is to what extent is the population characterized equivalently by those two

measures?

So these data show you for about 75 people who received either Menomune or Menactra, 75 in each group, how the fourfold rise rates compare to the 1:4 human complement rates. Those achieving a fourfold rise by baby rabbit are in green. Those achieving a 1:4 by human complement are in the pale yellow.

This is serogroup C. What you see here is that the results are very comparable.

If I can have the next slide please?

MEMBER SELF: Just to interject. That is group means rather than the association between those two assays. So what would be really interesting, I think, would be to look at the scatter plot of the titers, one assay versus the other for subgroup C. And if the data were available for the other relevant subtypes.

DR. DECKER: The analysis you are requesting was conducted by the FDA statistical analyst and is present in the FDA's briefing document. But I'd respectfully suggest that that's not the most important question for this use of the assay because

we're not seeking to validate the baby rabbit assay as a diagnostic tool for individual patients.

And we actually have no interest in whether or not it produces the same result for an individual as does the human complement. Rather we're using this as a probe to test a population to see if it gives us the same predictive ability in a population as does the human complement.

And, therefore, the scatter plot, which frankly doesn't look very good, would be misleading because it's only on the population level that these two perform very, very similarly. So that's why I'm showing you population data.

MEMBER SELF: Yes. I guess what you could find from that scatter plot would be you could identify the range of the baby rabbit assay titers that is induced by the vaccine. And then look up to see that essentially all or, you know, what fraction of those meets the 1:4 criterion for the human complement assay that then has the connection to the risk data.

DR. DECKER: Yes, and that would be

entirely appropriate if the goal was to validate that assay's sensitivity and specificity as applied to individuals. But --

MEMBER SELF: I guess we'll disagree.

CHAIRMAN OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: Yes. David Markovitz. I had another -- one comment and one question.

First of all, the comment is when you look at the racial makeup of your subjects, it doesn't really reflect very well the makeup of the United States on a percentage basis. And I guess on a gut level, I doubt that's going to matter in terms of the results.

But I would like to suggest that future studies try to have a little closer approximation because that will give us -- get more faith that the data reflect what will happen to the United States population.

My second question, which is not certainly essential to the process here but I'm very curious why it is that we don't have, you know, serogroup B included in any of these vaccines. Can you give me

some background on what's going on with that? And what are people trying to do to rectify that problem?

DR. DECKER: Let me respond to both of your comments.

With respect to the racial/ethnic distribution of the participants in the studies, there were 14 percent who were not white, non-Hispanic, which is less than the distribution of the U.S. population but more than historically we've been able to achieve in studies. And I think what you've seen, as candidates come forward here over the years, is that number is creeping up.

Everybody is trying to bring that up in alignment. But it's a lot harder to get participation in inner cities and so on in study recruitment. And so it's a difficult process. And all I can say is it's improving.

I can also tell you that subgroup analyses by race showed no worrisome deviations in the response rates. In fact, the Blacks and the Hispanics and so on tended to have higher immune response rates than the white. And so we find no evidence to suggest that

there is a concern there.

With respect to the second and really compelling question why not B, the fact is that one cannot have a polysaccharide-based vaccine for B because the polysaccharide of B is the same polysaccharide that's involved in neural coding in the human nervous system.

And so if a vaccine of B worked, it would be an effective vaccine against your own nervous system. But it won't work because you are tolerant to that.

Now that means the pathway for a vaccine to B has to lie through protein types but there are nearly 100 protein types for B. So in the world right now, there are only a couple of vaccines against B. And they're only known to work on isolated island situations where they -- they don't work on continental masses because on an island, you can a single dominant protein type.

So the Cuban vaccine probably does work in Cuba. And the recently-developed vaccine for New Zealand is specifically targeted to the protein type