FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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OPEN SESSION

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THURSDAY,
NOVEMBER 17, 2005

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The open session of the conference convened in the Versailles Room of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, MD 20814, at 10:18 a.m., pursuant to notice, Gary D. Overturf, M.D., Chair, presiding.

COMMITTEE MEMBERS PRESENT:
GARY D. OVERTURF, M.D., Chair
MONICA M. FARLEY, M.D.
RUTH A. KARRON, M.D.
PHILIP S. LaRUSSA, M.D.
DAVID MARKOVITZ, M.D.
CINDY LYN PROVINCE, R.N., M.S.N., M.A.
STEVEN SELF, Ph.D.
WALTER ROYAL, III, M.D.
BONNIE M. WORD, M.D.
FDA STAFF PRESENT:
CHRISTINE WALSH, R.N., Executive Secretary

CONSULTANTS:
SETH HETHERINGTON, M.D.
LISA JACKSON, M.D.
PAMELA MCINNES, D.D.S.
STEVEN PIANTADOSI, M.D., Ph.D.
ROBIN ROBINSON, Ph.D.
MARK STEINHOFF, M.D.
MELINDA WHARTON, M.D., M.P.H.

I-N-D-E-X

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

10:18 a.m.

CHAIR OVERTURF: I'd like to call the open session back to order.

At this point we will call the open session to order, and the first presentation is going to be by Dr. Pratt. Before we do that, I need to call on Christine Walsh for certain administration matters.

SECRETARY 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 all of you to this meeting of the Advisory Committee.

The remainder of today's session will constitute of presentations that are open to the public.

I would first like to request that everyone please check your cell phones and pages to make sure they are off are in silent mode.

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

meeting.

This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on November 16th and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on November 17, 2005. This announcement addresses conflicts of interests for the discussion of Topic 2 on the development of new pneumococcal vaccines for U.S. licensure for adults. In accordance with 18 USC Section 208 B(3) waivers have been granted to Drs. Ruth Karron and Steven Piantadosi. A copy of the written waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Dr. Seth Hetherington is serving as the industry representative acting on behalf of all related industry and is employed by Inhibitex, Incorporated. Industry representatives are not special government employees and do not vote.

With regards to FDA's guest speakers, the

Agency has determined that the information provided by these speakers is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Matthew R. Moore is a medical epidemiologist, National Center for Infectious Diseases, CDC, Atlanta.

Dr. Sandra Steiner is a microbiologist/immunologist, Division of Bacterial and Mycotic Diseases, CDC, Atlanta.

As guest speakers they will not participate in the Committee deliberations or will they vote.

In addition, there are regulated industry speakers making presentations. These speakers may have financial interests associate with their employer and with other regulated firms. The FDA asks that in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts

of interests.

This conflict of interest statement will be available for review at the registration table.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the sponsor, its product and if known, it's direct competitors

That reads the reading of the conflict of interest statement and, Dr. Overturf, I turn the meeting back over to you.

CHAIR OVERTURF: For this session I'd like to call the open session again to order. And I would like to have the members of the Committee and the consultants introduce themselves. We'll start with Dr. Wharton.

DR. WHARTON: Melinda Wharton, National Immunization Program, Centers for Disease Control and Prevention.

MEMBER SELF: Steve Self, Hutchinson Cancer Research Center at the University of Washington.

DR. JACKSON: Lisa Jackson, Group Health Cooperative, Seattle and University of Washington.

MEMBER KARRON: Ruth Karron, Johns Hopkins University.

DR. PIANTADOSI: Steve Piantadosi, Johns Hopkins School of Medicine.

DR. STEINHOFF: Mark Steinhoff, Johns Hopkins University.

MEMBER WORD: Bonnie Word, Baylor College of Medicine, Texas Childrens Hospital.

MEMBER LaRUSSA: Philip LaRussa, Division of Pediatric and Infectious Diseases, Columbia University.

DR. ROBINSON: Robin Robinson, Office of Public Health Emergency Preparedness, U.S. Department of Health and Human Services.

MEMBER PROVINCE: I'm Cindy Province, I'm the consumer representative on VRBPAC. And I'm with the St. Louis Center for Bioethics and Culture.

DR. McINNES: Pamela McInnes, National Institute of Allergy and Infectious Diseases, NIH.

MEMBER FARLEY: Monica Farley, Emory University, Department of Medicine, Infectious Diseases.

MEMBER ROYAL: Walter Royal, University of Maryland School of Medicine, Department of Neurology.

DR. HETHERINGTON: Seth Hetherington. I'm the industry representative and the Chief Medical Officer of Inhibitex outside of Atlanta, Georgia.

MEMBER MARKOVITZ: David Markovitz from the University of Michigan.

CHAIR OVERTURF: And I'm Dr. Gary Overturf from the University of New Mexico School of Medicine and Chair of VRBPAC.

Our first presentation for the open session this morning is from Douglas Pratt from the FDA.

DR. PRATT: Good morning. I'm Douglas

Pratt from the Division of Vaccine and Related Products Applications, Office of Vaccines, Biologics Evaluation and Research.

I'll begin the CBER presentation by reviewing some of the regulatory history of the license 23 valent pneumococcal polysaccharides vaccine, PNEUMOVAX, which is manufactured by Merck.

I will then present a few possible scenarios for clinical efficacy studies for adult indications with approximate samples sizes.

And in certain situations immunologic endpoints can be used to infer efficacy for licensure purposes. I will discuss briefly the use of the opsonophagocytic antibody assay in this context.

And finally, I'll discuss additional items for the Committee's consideration, including the accelerated approval regulations.

PNEUMOVAX 23 is the only vaccine currently licensed for use in adults for prevention of pneumococcal disease. It is made up of 23 of the most common pneumococcal serotypes that cause disease in humans. At least 90 capsular serotypes have been

identified, but 23 serotypes in this vaccine are thought to cover serotypes that cause approximately 85 to 90 percent of invasive disease in humans.

An earlier version of this vaccine was first licensed in 1977 as a 14-valent vaccine that contained 50 milligrams of polysaccharide for each serotype. The vaccine was later reformulated to include additional serotypes at reduced antigen content. The 23-valent formulation was licensed in 1983.

PNEUMOVAX is labeled for routine use in adults over the age 50 years. This differs from recommendations of the Advisory Committee on Immunization Practices that recommended routine use in adults 65 years of age and older.

The indication and use section of the PNEUMOVAX label states that the vaccine is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine. This indication does not separate out invasive disease from noninvasive disease. And as will be shown in the next slides, this is consistent with the primary

endpoint in the support of efficacy studies conducted in South Africa.

The remainder of the indication in the usage section of the label is largely a restatement of the ACIP recommendations. Recommendations for use in immunocompetent persons two years of age and older include persons with certain cardiac, pulmonary, liver disease, persons with asplenia and persons living in special environments.

Recommendations are also made for persons older than two years with immunocompromising medical conditions.

Studies conducted in South Africa by Schmidt and colleagues provided the principal basis of efficacy for the polysaccharide vaccines at the time of licensure. Results of two South African studies, one using a 6-valent vaccine and another subsequent study using a 12-valent vaccine were provided in the license application.

Efficacy results for the 12-valent vaccine are show in this slide. Note that the mean age for subjects in this study was 22 years. Duration of

follow-up for case ascertainment was approximately one year.

The primary endpoint was pneumococcal disease due to vaccine serotypes. Confirmation of vaccine serotype was by blood, sputum or nasopharyngeal culture or by mouse inoculation. And the study report stated that sputum was the sample used in the mouse inoculation test. In fact, in the study none of these cases from any of the study groups was confirmed by a blood culture.

The efficacy estimate, 91.7 percent, was determined by comparing against the combined placebo meningococcal A&C vaccine controls. Noteworthy is the attack rate in the control groups which exceeded 22 per 1,000 or 2200 per 100,000.

Two serotypes were subsequently added to the 12-valent formulation prior to licensure of the 14-valent.

Well, after licensure of the 14-valent vaccine pneumococci of other capsular serotypes were recognized as important causes of pneumococcal disease. The manufacturer was asked to reformulate to

include additional important serotypes.

Due to concerns about the amount of bacterial polysaccharide in a 23-valent product, formulations of lower polysaccharide antigen content were studied. In the study submitted to the license application to support the formulation change, healthy subjects 21 to 64 years of age received a 22-valent product containing either 50 or 25 micrograms per serotype. The immune response were determined by a 2-fold Rise in the antibody titer is measured by radioimmunoassay. Responses of the two groups were judged as essentially the same and the safety profile was also judged as acceptable.

Prior to licensure Type 33F was added to the license formulation.

Well as noted previously, the supportive efficacy studies for the polysaccharide vaccine were conducted in young South African gold miners. Among the elderly and other high risk groups studies have yield mixed results. Provided in the briefing materials for the Committee as copies of reviews with meta-analyses discussing some of these results.

The ACIP recommendations for routine use in persons older than age 65 is based on case control studies evaluating invasive disease citing effective estimates that range from 56 to 81 percent.

Effectiveness for non-bacteremic disease in the elderly has not been convincingly demonstrated. Again, the ACIP statements cites a lack of specific and sensitive diagnostic tests for non-bacteremic pneumococcal pneumonia as a possible reason for the inability to detect a vaccine effect.

While it's not my intention to discuss exhaustively the various studies and results regarding the effectiveness of the polysaccharide vaccine, but two relatively recent studies addressing efficacy for groups included in the ACIP recommendations and in the labeled usage section of the label deserve mention and are cited on this slide.

In a large retrospective cohort study of more than 47,000 persons over age 65 conducted by Dr. Jackson and colleagues, effectiveness of the vaccine and preventative invasive disease was estimated at 44 percent. However, no effect on all cause pneumonia

was demonstrated.

In a randomized controlled trial conducted in Uganda among adults infected with HIV, the vaccine was ineffective against invasive disease and all pneumococcal outcomes. And, in fact, was associated with a significant increase for all cause pneumonia.

Prospective randomized control trials provide the best evidence of clinical effectiveness. The choice of efficacy endpoints for any vaccine and the clinical efficacy trial should be guided by what is most clinically meaningful. Clinical endpoints in vaccine trials should provide evidence of benefit to the individual. Thus, indirect effects such as hurt immunity have not been used as a primary basis of efficacy.

Also cost effectiveness outcomes are not endpoints suited for regulatory decisions.

Feasibility of the studies in terms of cost is not a judgment for FDA, although FDA reviewers recognize the practical issues associated with the choice of endpoints. Vaccine manufacturers and sponsors of the vaccine trials will ultimately decide

the kinds of studies that are feasible from their perspective.

Well, in thinking about possible clinical trial designs to establish efficacy of a new pneumococcal vaccine in adults, age of trial for participants requires careful consideration. Adults over the age of 65 years are considered high risk of pneumococcal disease and so represent one of the most relevant populations in which to determine vaccine effectiveness. However, because the polysaccharide vaccine is recommended for routine use in all persons over age 65, it might be considered unethical to withhold or delay vaccination with the licensed vaccine in order to conduct a randomized placebo controlled trial in this population.

The age group of persons 50 to 64 years old is at moderately high risk for pneumococcal disease. And this group also includes individuals with other risk factors that put them at high risk. A placebo controlled trial in this age group may be feasible and would not be associated with the same concerns about withholding a recommended vaccine.

However, an efficacy study in this population may not accurately predict effectiveness in the higher risk groups.

A few scenarios of possible clinical endpoint studies are presented in the slides that follow. Each of these scenarios considers persons 50 to 64 years of age in placebo controlled studies. Endpoints considered include invasive pneumococcal disease, all cause community acquired pneumonia and presumptive pneumococcal pneumonia.

A number of assumptions are necessary to estimate the sample sizes and different statistical programs may yield different sample size estimates. To construct these scenarios it was assumed that studies were placebo controlled, randomized one-to-one and studies would provide for a mean follow-up of 22 years per case ascertainment.

Also within each scenario sample sizes are provided for a vaccine with serotype coverage of about 60 percent, which might approximate a conjugate vaccine coverage another set of sample sizes for a vaccine with more broad coverage, such as is provided

by the 23-valent vaccine.

Ninety percent power was used to manage the risk of a failed study due to inadequate sample size.

Well critical to the sample size calculations is the expected background rate of pneumococcal disease. For this scenario a lower rate of 25 per 100,000 was chosen. This approximates a rate of 20 per 100,000 cited by Whitney et.al. in 2003 for a wider age range of 40 to 64 for adults in the U.S. Of course, the epidemiology in the U.S. continues to change, as well be discussed later by Matt Moore of CDC.

A higher rate is also presented 50 per 100,000 because it may be possible to identify populations with other risk factors such as smoking history, asthma or membership in a high risk ethnic group or which identify populations outside the U.S. with higher rates of pneumococcal disease.

This table provides the estimates sample size per group for the various assumptions. These values are not intended to be precise, but only to

provide an idea of the scale of the studies that would be required. To walk through an example at the top of the table for an assuming of the lower background rate of 25 per 100,000 due to all pneumococci, and assuming 60 percent vaccine coverage with a true efficacy of 70 percent, the study would require 82,000 subjects per group.

And at the other end of the spectrum using a higher background rate of 50 cases per 100,000 with a broader vaccine coverage of 85 percent and true vaccine efficacy of 90 percent each group would require 16,000 subjects.

It can also been seen that doubling the background rate reduces the sample size by half for the scenarios that are otherwise the same.

All of these efficacy estimates have relative robust 95 percent lower limits on efficacy which are well above zero excepting a lower lower bound prolonging follow-up for case ascertainment and broadening the serotype coverage would all lower the samples sizes for this endpoint.

Typical vaccine efficacy studies have used

specific case definitions that rely on identification of the disease causing pathogen, usually by culture methods. Such definitions provide high efficacy estimates for effective vaccines. So called effectiveness trials evaluate less specific endpoints for which the pathogen is not identified. A relevant example for our discussion would be the endpoint of all cause pneumococcal pneumonia.

Effectiveness studies have supported vaccine indications in the past and a relevant example was the effectiveness trials supporting an indication for the approval of Flu Mist for adults 18 to 49 years of age. The indication for use in adults was based on clinical definitions consistent with the diagnoses of influenza but not confirmed as influenza by virus culture. Note the efficacy estimates of 11 to 24 percent for prevention of these influenza syndromes.

These data were judged adequate to support the use of FluMist in adults 18 to 49 years of age, however for this vaccine efficacy had also been demonstrated for culture confirmed disease in young children.

So in this second scenario an effectiveness endpoint of all cause community acquire pneumonia is considered a background of community acquire pneumonia of 300 to 600 per 100,000 is used. Data on community acquire pneumonia in this age group is actually difficult to obtain. These numbers are based on a study by Marst et.al., a study in Ohio for the age range of 40 to 64 years of age, and then rounded upwards slightly to 300 per 100,000 for the 50 to 64 age range.

A similar background rate can be estimated by back calculating from the rate of invasive disease, assuming four to five cases of pneumonia for each case of invasive disease, and that about 30 percent of all pneumonia resulting in hospitalization is due to pneumococcus. Using other assumptions as before, these are the sample sizes that would be required.

The derived efficacy estimates for all cause pneumonia are low as expected here ranging from 30 to 23 percent.

Sample sizes are quite large for some of these assumptions. Nevertheless, such studies might

be feasible in populations with higher background rates and with a vaccine with broad serotype coverage. Such studies could be conducted simply by making use of automated databases and should not be resource intensive.

Well, identifying pathogens causing non-bacteremic pneumonia with a high degree of certainty can be difficult. Isolation of pneumococci from the upper respiratory tract is not a guarantee that the bacteria is causing lower respiratory tract disease as pneumococci can be part of the normal upper respiratory flora. Nevertheless, clinical radiologic and microbiologic information guide treatment of suspected pneumococcal pneumonia in the clinic. And as note earlier, the bulk of the data supporting efficacy of the original South African gold miner studies in pneumococcal disease and pneumonia confirmed by culture of the sputum.

Using additional diagnostic modalities, it seems likely that the specificity of the diagnoses can be increased. A commercially available urine antigen test for pneumococcal C polysaccharide is reported to

be highly specific with respect to blood, sputum and nasopharyngeal culture when used quantitatively.

Other urine tests specific for individual pneumococcal serotypes are under investigation.

Nonspecific markers of information such as C-reactive protein and procalcification have also been proposed as measures to improve the specificity of a diagnoses of bacterial pneumonia.

With a precise amount that the specificity of the diagnoses can be increased by these auxiliary methods is not clear, and we choose not to account for the specificity in the sample size estimates that follow.

Let me back up to get to the background rate used in this scenario. The background rate of 100 to 200 cases per 100,000 is used. This is based on estimating one-third of the hospitalizations due to community acquire pneumonia in the previous scenario would be to pneumococcus. And then again this rate can be arrived at by back calculating using the similar assumptions from the rate of invasive disease.

So these are the sample size estimate for

an efficacy trial for an outcome of presumptive pneumococcal pneumonia. Lower efficacy might be expected for pneumonia compared bacteremia, so assumed efficacy was lowered in these estimates to range from 60 to 80 percent as opposed to 70 to 90 percent of this table. A true efficacy of 90 percent would require smaller sample sizes.

Low sensitive and low specificity for the diagnoses would tend to increase the sample size. Higher background rates of pneumococcal pneumonia, more broad serotype coverage and longer follow-up for cases and a less stringent lower bound on the efficacy estimate would reduce the sample sizes.

Due to the diagnostic workup and logistics of such a study it could be relatively more recourse intensive per subject than the previous scenarios.

Some concepts for trails in older adults are outlined in the following two slides, as discussed previously conducting placebo controlled studies in the elderly might be difficult, in part, because of the ethical concerns about withholding a recommended vaccine. And it's not clear that any of these studies

could be done. However, in a well monitored study a decision to delay vaccine with the polysaccharide might be viewed as acceptable by IRBs and subject given that the current recommendation is to give polysaccharide vaccine only once. There's some uncertainty about the efficacy in this age group and if concerns about hyporesponsiveness following the polysaccharide vaccine are valid. Background rates of disease are higher in this population, so sample sizes would be smaller, studies more feasible and this is certainly a relevant population to study a vaccine.

So the first scenario would be a placebo controlled study of the new vaccine against a placebo.

The second scenario, the second concept for a new vaccine would be to add the new vaccine onto a background of 23-valent vaccine in an attempt to assess added or the existing therapy. Such a study would not have the ethical concern about withholding or delaying vaccine with the 23-valent polysaccharide.

For an invasive disease endpoint sample sizes could be prohibitive since polysaccharide vaccine is effective in this population. However,

since efficacy of the polysaccharide vaccine for non-bacteremic disease is apparently quite low and possibly similar to placebo, comparative studies to evaluate non-bacteremic disease might be feasible. And this would, certainly, be a highly relevant outcome.

And the third design concept to new vaccine would be compared head-to-head against the 23-valent polysaccharide vaccine. For a low efficacy estimate such studies would be quite large.

And then in a fourth design for consideration, this would be a three arm study that combines concepts one and three. It would be powered to provide stand alone efficacy relative to placebo and would have the 23-valent polysaccharide as a control to check against unexpected outcomes such as a lower efficacy than might be expected for the license vaccine alone. But we do not attempt sample size calculations for these additional four scenarios, and they're presented here for your consideration.

In certain situations efficacy of a new vaccine can be inferred from an immune response that is similar to that induced by a licensed vaccine for

which efficacy has been demonstrated. A recent example of this approach was the licensure of Menactra, a quadrivalent meningococcal conjugate vaccine which was approved based on immunologic non-inferiority compared to the licensed polysaccharide vaccine Menomune, both of which are manufactured by Sinofi Pasteur.

Such an approach is also consistent with advice provided by the 2001 VRBPAC regarding approval pathways for new pneumococcal conjugate vaccines in infants. For infants, the comparative assessment of antibody concentration using a standardized ELISA was judged acceptable. However, antibody levels that may be useful in children for non-inferiority comparisons for inferring efficacy would likely not be valid for adults, many of whom have preexisting antibody to some or most serotypes. And the level serum antibodies that correlate with protection in adults and elderly have not be determined.

Evaluation of an effective immune response in adults is thought to be more dependent on serum opsonophagocytic antibody titers.

Opsonophagocytic antibody is a measure of functional antibody that is thought to be central to protection against pneumococcus for vaccines directed at capsular antigens. Details of the assay will be discussed later by Dr. Sandy Steiner, but in brief antibody lining to the bacterial surface with complement is taken into phagocytic cells and a serum titer of opsonophagocytic antibody can be determined in this assay. The in vitro assay is thought to provide evidence of in vivo protection. However, some unknowns remain. Protection from disease will depend not only on function of the antibody, but also function of the phagocytic cells. And it's not clear that the phagocytic cells of the elderly and other high risk populations will function similarly to the cultured phagocytic cells used in the assay.

Also, the quantitative relationship of the OPA that correlates with efficacy as determined in clinical trials has not been established. It's also the quantitative relationship may differ by disease endpoint; that is the amount of antibody needed to protect against an invasive disease may differ from

the amount of antibody needed to protect against pneumonia.

With a regulatory pathway using demonstration of non-inferior immune response to that of a licensed vaccine is problematic when the new vaccine has fewer serotypes. Evaluation for common serotypes could actually be straightforward, but the comparison to the licensed vaccine, the new vaccine would fail on comparisons to those serotypes that are only in the 23-valent vaccine. One is left with the problem of how to account for the serotypes that are not included in the new conjugate vaccine but present in the polysaccharide vaccine if one follows the pathway of comparison to the licensed product.

Well, to compensate for fewer serotypes it may be argued that the conjugate vaccine offers theoretical advantages of the superior immune response over that of the licensed product for serotypes in common. Such higher antibody levels that are opsonophagocytic antibody activity or lack of hyporesponsiveness. In this regard criteria for demonstrating a superior immune response have not been

developed for regulatory purposes. It's not clear how much additional opsonophagocytic antibody would be needed to be meaningful. Evidence is lacking that higher antibody levels of OPA result in greater protection.

A regulatory decision to attribute vaccine benefit based on an immune response that is superior to that induced by the licensed vaccine would be a novel approach to licensure, and this approach would need scientific consensus and VRBPAC advice.

Conjugate vaccines would still need to be used in conjunction with the 23-valent vaccine to assure immunization for all 23 types in the 23-valent vaccine. Use of the conjugate vaccine in conjunction with the 23-valent vaccine would raise some additional regulatory concerns, such as how the vaccines would be labeled. There are specific regulations addressing labeling of products to be used on combination.

Also, if a conjugate vaccine is to be used before a polysaccharide vaccine, that could have labeling implications for the licensed product, PNEUMOVAX, and it's also uncertain what the regulatory

status of the new product would be if for some reason the 23-valent vaccine were to become unavailable and whether additional studies would be needed at that point in time to support a stand alone licensure.

Well, for vaccines targeting noncapsular antigen an immunologic efficacy is not possible since preventative efficacy of these new vaccines has not yet been demonstrated. Also, it's not clear if they will be able to induce functional antibody. Thus, it appears that a clinical endpoint efficacy study will be needed for vaccines targeting noncapsular antigens. With broad serotype coverage anticipated from such vaccines clinical endpoint efficacy studies would be more feasible.

Indirect effects of vaccination after introduction of Prevnar are thought to be due to prevention of colonization and carriage in the nasopharynx of children resulting in reduction of transmission to older adults. Clinical studies designed to evaluate colonization would provide clinical evidence of a vaccine effect. However, since colonization is an asymptomatic condition it's

prevention offers no direct clinical benefit to the vaccine participant.

Prevention of colonization or carriage has not previously been used as a primary clinical endpoint to support licensure decisions. Use of nasopharyngeal colonization or carriage as the primary efficacy basis of approval would need acceptance as a surrogate of efficacy. Studies to evaluate nasopharyngeal colonization, however, would likely be feasible.

Finally, I'd like to talk a little bit about the accelerated approval regulations. Accelerated approval regulations provide a regulatory option for certain products intended to treat or prevent severe and life threatening conditions. Under the accelerated approval regulations a product can be approved based on a surrogate of efficacy. The level of evidence required of the surrogate is that is reasonably likely to predict clinical benefit. The new treatment must offer meaningful benefit over existing treatments.

Another necessary condition under

accelerated approval is that a confirmatory clinical study, clinical endpoint study validating the surrogate must be conducted post-licensure. Confirmatory studies should be well underway at the time of the accelerated approval.

The accelerated approval regulations have been used only once in vaccine development, and that was for the recent approval of Fluarix, trivalent inactivated influenza vaccine made by GlaxoSmithKline. Hemagglutination inhibition antibodies served as the surrogate in that case.

It seems likely that pneumococcal conjugate vaccines for the elderly could meet the conditions of accelerate approval using opsonophagocytic antibody as a surrogate.

So in summary new pneumococcal vaccines for use in adults and the elderly are being developed by multiple manufacturers. Evidence of effective to support licensure might be based on clinical endpoint efficacy studies or immunologic criteria such as opsonophagocytic antibody.

Advice of VRBPAC is being sought regarding

the most appropriate endpoints, trial designs, study populations to support licensure of a new pneumococcal vaccine for adult indications.

And I'd like to acknowledge my colleagues.

CHAIR OVERTURF: There will be time for questions after three presentations, so we will hold those questions at this point and proceed to the next presentation, which is Sandra Steiner on opsonophagocytic activity.

DR. STEINER: Good morning. Thank you very much for the invitation.

I hope to talk to you about the functional antibody activity as measured by opsonophagocytosis.

At any given point in time the host, the human host, can a variety of antibodies present in circulation that are specific to pneumococcus. They can be present there by a number of factors; either through disease, vaccination, passive immunization, colonization or possibly through cross reactivity.

In the laboratory we measure those antibodies by a variety of methods. The ones that you're probably more familiar with is the ELISA method

that gives you a microgram for a concentration is a quantitative measurement. However, we wonder how those antibodies actually work and do they actually confer some protection.

We have terms these concept functional antibody activity and there are functional determinations that are performed in the laboratory to measure these. One of them is animal protection studies where you do passive protection studies, and they're very difficult for those large trials that you have seen the numbers earlier on today.

The other one will be opsonophagocytosis, which I will explain in a bit of detail later on.

There are also indicators of memory that are used and these indicators are probably more important for the conjugate vaccines where you hope to have some prime -- and they are measured by antibody avidity. The antibody avidity is a modified ELISA assay. And you can also measure them by checking B-cells and finding out how well they assimilate when they encounter the antigen once more. And this is done by ELISA assays.

Concentrating on opsonophagocytosis and we can try to get the concept if we actually look at these two slides. Without the presence of antibody, you can see that the diplococci, the pneumococci are outside of the phagocytic cell. But in the presence of antibody these diplococci, the pneumococci actually get engulfed and they are present inside the phagocytic cell. When they're inside the cell, they're actually killed because they cannot survive inside that phagocytic cell.

So we need to find out how do we measure these and which are the players that actually carry out these functions inside the host. We have here the phagocytic cell that has a number of receptors on the surface for immunoglobulins and for complement. And the opsonins and the target bacteria. The bacteria will have a capsule on the surface that is specific of the serotypes, depending on what code they have on. The antibodies bind specifically to the surface of that capsule. And then once they bind, the complement will be deposited onto the surface of that bacteria. These bacteria is now opsonized and once it's

opsonized it's very amenable to that phagocytic cell. They will be engulfed. And once it is engulfed, it will be inside the phagocytes so many will be killed.

So about 12 years ago we started looking into a standardized way of doing this type of looks in opsonophagocytic assays. And we published a methodology for a single serotype measurement in which four components are present: The serum where you try to find out the function of those antibodies; the target bacteria; complement is one of opsonins, and; the culturable phagocytes which in our case we have been using HL60 cells differentiated into a polymorphonucleic cells.

As I mentioned before, once the pneumococci are internalized they are killed and what we actually measure is an opsonophagocytic titer.

In the laboratory when you're trying to determine these titers what you have is a series of unknowns serum that are run in duplicate. They are diluted, serially diluted and you have a quality controlled serum and immunoglobulins that are used as a reference. It is a gamma globulin preparation.

And what you do is you look at the killing that each of the samples will give and you compare it to the complement controls. Then you carry out the determination of the 50 percent or the dilutions that can give you at least 50 percent killing for the target period. And what you get are various titers being determined. It depends on what amount of antibodies are actually functional inside that serum sample how that titer varies.

Once you determine all those points for the various serum, what you have is a curve that you can actually draw. And you can do this by more advanced analytical analysis, like four parameter logistic curve regression analysis. This was data present by Tom Taylor in the lost pneumococcal meeting that we had in June of 2005. And there you can actually see that you can actually fit a curve that goes with the whole inflection. You can determine the midpoint of the curve and a continuous titer could actually be determined as well as you could also report a discontinuous titer.

So this particular assay has been

developed as a single serotype assay. But it's time consuming and is very reagent demanding. So efforts from Dr. Moon H. Nahm at the University of Alabama and in the Netherlands a Dr. Peter Hermans have allowed us to have a variety of other tests available that have two, four and up to seven different serotypes that can be measured simultaneously.

These are results presented at the pneumococcal meeting in June of 2005 by Mr. Burton where we have a correlation of the single serotype of opsonophagocytic assay with assays that were run simultaneous for four different serotypes in a multiplex format using viability as an endpoint. As you can see, there is a very good level of correlation for all the four serotypes that were tested. And there were probably two outliers or outside of the confidence interval, but overall the correlation is good, especially if you don't consider that particular outlier seen there.

They have also spent a great effort working on the automation of these assays. And we don't want to do these counts, because they're very

difficult to do manually. So they've worked on getting equipment that can actually do the counts in a fast throughput manner and be able to collect the data and graph it to be able to calculate the titers in a more speedious way.

We have also been working on eliminating the counts altogether. And we just recently published on a florescent methodology that we'll be able to eliminate the counts. And it's also done in a single and a multivalent format. These were using the strains that Dr. Debbie Bogaert had published in the Netherlands in her study from 2004.

There are a number of other assays that are also available for opsonophagocytosis. And we term them for convenience the update of opsonophagocytic assays.

The uptake OPAs are primarily through flow cytometric methods and they measure the uptake of kill bacteria or polysaccharide coated particles. They can be available in a single serotype or in a multivalent format also with up to four different serotypes measured at the same time.

The flow cytometric assays do target a population of the effected cells, so you're actually looking at the phagocyte. And then you look at the shift in the fluorescence of that population of cells to the right once they have been uptake of the fluorescent particals. So that generates a curve of data similar to the ones that we had for the killing assay. And you can also calculate the 50 percent point and determine the titer.

Again, as I mentioned, I could be done in the monovalent format, I mean has it various levels of correlation to the single serotype assay, viability assay or in a multivalent format.

So you're probably wondering what is the current validation status of all these assays. And for the single serotype killing assay, I'm glad to say that we have developed standardized, evaluated and validated at the GLP level thanks to the efforts of the entire scientific community.

For the other assays it's a different story. They have only been developed and standardized. So there's a lot of work to be done there, especially

to be able to multiplex.

Some of the data that I will be giving you later on is related to the efforts that lead to the evaluation and validation of the single serotype of opsonophagocytic assay. These are results from a laboratory evaluation that we did once the technology was transferred to the various laboratories across the world. And they participated in a multi-laboratory evaluation with a panel of quality control sera that was evaluated for at least seven different serotypes. We counted exceptions that are highlighted here in yellow. Most of the sera were overall with a 75 percent branding only one dilution away from the median titer. And 88 percent of them were two dilutions away from the median titer.

When we look at how well were those titers being hit depending on the sera type, the particular sera type or depending on the titer, I'm just giving you here the results for serotype 14. We noticed that it was easier to get an agreement between laboratories if the titers were low. Right here is a titer of only four. But if the titers are higher, then there is

more of a variability along each of the serum samples with the defined titer that is being reported. So it's harder to hit higher titer than a lower titer.

The validation efforts have been done primarily by industries, since they have been able to apply this technology in their hands. And this is studies that was just recently published by Brenda Hu from Wise Laboratories. And they have been able to report the specificity of the assay to be greater than 80 percent. And notice that only a heterologous Ps could only give less than 20 percent reduction of the signal.

The intermediate precision was determined to be overall 81 percent for all the titers to be 2 dilutations away from the median.

And the linearity for 9 serotypes evaluated was fairly good, between .98 with very good slopes, also around 1.

The accuracy for nine serotypes was 100 percent for seven of them, but for two of them it was slightly lower.

And overall, they determined that the

assay was fairly robust.

And maybe what you have been waiting for is how is this correlating with protection. I will give you selected information that is more related to how we have derived these to be a potential correlate for protection.

The ELISA correlation in healthy populations, the passive protection in animals and the minimum level needs for vaccine efficacy in infants as follows, and I will give you a little bit on the elderly what we know.

For the ELISA, these are results of the adults following 23-valent polysaccharide vaccine, recipients of that vaccine. And we see a correlation between ELISA and opsonophagocytic titer that is fairly high. This is all serotypes combined. You will be able to see results like these for many, many studies that are present in the literature. And the correlation is very good in infants. And as you start working with normal healthy adults, but as you start working with populations that are more at risk and the very elderly the correlation with ELISA is not as

good.

The protective level in mice that was determined in a study presented by Johnson in 1999 demonstrated that you could protect against non-bacteremia. Seventy-five of the mice could be protected against bacteremia with a titer, a opsonophagocytic titer of eight.

And this is a study from infants and is based on the Northern California Kaiser Permanente trials for the vaccine. And in this particular graph you can see a reverse cumulative distribution of children that have had an antibody concentration involve a particular level that is listed in the X axis.

And what we can see here is that 97.9 percent of the vaccinated population had at least .2 micrograms per mil in concentration in their serum while only 12.9 percent of the control population had that particular titer.

This study was also used to help compare the values with the opsonophagocytic titers and help us define what will be the minimum opsonophagocytic

titer. And in here you can see the correlation between the ELISA concentration -- I apologize for that. And the opsonophagocytic titer. And what you can see in these quadrants is at .2 micrograms per mil concentration actually corresponds to a titer of 8. And that discriminates clearly between the recipients of the conjugate polysaccharide vaccine and those that are the controls. This study was published by Jodar in 2003 in *Vaccine*. However, this is a minimum value with a correlate of for opsonophagocytosis only in infants.

What do we know about dysfunctional antibodies in the elderly? The studies are being performed right now and a lot of these studies actually have not been published yet. But for what I can tell you is that the protected levels are unknown, as you heard in the first talk, too. That we don't know the ELISA or the opsonophagocytic titer that will actually correspond to protection in elderly or in other populations at high risk.

We did study in 1999 before ELISA had absorption of antibodies where we found that there was

a reduction in the function of the antibodies that were eliciting the elderly after receiving the pneumococcal polysaccharide vaccine 23-valent. And the reduction was more notorious or more prominent in the very, very elderly; people that were 80 to 89 years of age and if they were greater than 90 years of age. We attributed these to a lower avidity in the antibodies. And we saw a very poor correlation with ELISA with the exception of serotypes 14 where we had a .8 correlation. And these antibodies did not protect in mice.

In the year Usinger and Lucas did a very elegant study with avidity and function. And they also looked at adult serum with polysaccharide vaccine and they confirmed the relationship between avidity and function and that you're required to have high avidity in the antibodies in circulation to be able to have function, opsonophagocytic function in those antibodies. Those antibodies will be the ones that will protect in mice.

And just recently we with the collaborators in Toledo, Ohio, Dr. Westerly Slabb,

we've been able to show that in elderly a lot of those antibodies are cross reactive. And when you absorb them with additional -- the absorption -- like with 22F polysaccharide, you can reduce the signal that is being measuring the ELISA. And that they still produce opsonophagocytic activity in the elderly, in this case where people higher than 77 years of age.

We need very large scale studies that can address and look at all these issues. And I know some of these studies are underway, and probably very soon to be published. So, hopefully, we will have more information available.

The clinical studies that have used these opsonophagocytic assays are mostly outside of the U.S. have been done by the Finns. As these are results from presentations that Nina Ekstrom presented at the pneumococcal meeting in June 2005. And without going into detail in all of them, you will be able to see that they have evaluated a lot of the conjugate vaccines that are being worked with for trials. And they work in Finnish children, in African, in populations in Israel, and also in Filipino

populations. And they've used primarily the killing of opsonophagocytic assays single serotype, but they also are starting to use the flow cytometric opsonophagocytic assay in some of their trials.

So here are advantages of what we are doing here with opsonophagocytosis is because we will have a laboratory correlate of protection. And it could potentially reduce the numbers of efficacy studies that need to be done. And also we have a method available that has been worked out all the way to the GLPs or the good laboratory practice level that is the killing single serotype OPA.

We have information about the assay and strains and references available at the website that is maintained by Dr. Moon H. Nahm at the University Alabama. He has standardized, validated. He used culturalable phagocytes to eliminate the variability between donors.

His high throughput can be done at high performance conditions and it can be used for data analysis that is more sophisticated.

The disadvantages of using an

opsonophagocytic assay, of course, is no matter what we face still in vitro correlate. And it requires laboratory facilities, the training of technical staff. And we need a lot of information regarding multiplex assays before they can be used for these type of assays for studies.

Thank you very much.

I would like to give thanks for inviting me here today and to all of my colleagues at CDC for helping me with this.

Thank you.

CHAIR OVERTURF: Thank you.

We'll proceed with the last presentation of this morning, which is Matthew Moore.

DR. MOORE: Good morning. I'd like to thank the Advisory Committee for the opportunity to talk with you this morning about the epidemiology of invasive pneumococcal disease in adults.

I think before I get too far into that, I need to spend a little time talking about the epidemiology in children because I think it's very instructive in helping us to think about or to

construct a framework for thinking about the effects of a new vaccine in adults. So first I'm going to review the direct effects of the seven-valent conjugate vaccine in children both in terms of the direct effects and then the indirect. And I'm also going to talk a little bit about replacement disease. Then I'll move on and talk about the indirect effects of PCV7 among adults by age group, by syndrome and by underlying disease status. Toward the end I'll get in a little bit to what we might expect in terms of serotype coverage in adults for different conjugate vaccine formulations as well as the 23-valent polysaccharide formulation. And then I'll just end very briefly on opportunities for evaluations of new vaccines in adults.

So let's talk about children first. Many of you in the room are familiar with this surveillance program called Active Bacterial Core Surveillance or ABCs. This is a laboratory-based, population-based surveillance system that operates in several areas around the country. For the purposes of this discussion I'm going to focus on the areas highlighted

in yellow here which were under continuous surveillance from 1998 through 2004. And although some areas are highlighted in their entirety, I should point out that for example in the state of California it's really only one county that was under continuous surveillance. The state of Connecticut, on the other hand, was under continuous surveillance for the entire state for this whole period.

ABC's methods are relatively straightforward although pretty labor intensive. Our case definition includes streptococcus pneumonia isolated from a normally sterile site, such as blood as cerebral spinal fluid.

For each case a chart review is performed, and this is a very labor intensive process that's conducted by our state health department and our academic partners.

The epidemiologic data are aggregated at CDC, but then the individuals isolates are also sent to reference laboratories for serotyping, susceptibility testing and genetic testing using a method called multi locus sequence typing which I'll

talk about in a few minutes.

For the purposes of this discussion I'm going to spend a lot of time talking about rates of disease expressed as cases per 100,000 population broken down into these age groups highlighted in yellow. Again, this is going to be using the sites that were under continuous surveillance from 1998 through 2003, which is approximately 17 million persons in the U.S. All of these changes are going to be expressed as percentage increases or decreases with 95 percent confidence intervals so you can get a sense of what is statistically significant.

At the end I'll talk a little bit about the vaccine type invasive disease cases that were directly and indirectly prevented based on these data.

So this is the first slide showing along the X axis the calendar year of observation and along the Y axis the incidents of invasive pneumococcal disease in children under the age of 18.

The yellow line at the top highlights children under the age of 5. Obviously, these were targeted for vaccination. And the green line way at

the bottom indicates children aged 5 through 17.

You can see that in 2001 the vaccine was introduced and following that there was a 77 percent decline in invasive pneumococcal disease in children under the age of 5 from 1988 through 2004.

In older children, age 5 to 17, there was a 42 percent decline, and this was also statistically significant. So the next question might be well how much of this is actually attributable to the 7-valent conjugate vaccine? And one way to get at that question is to only look at rates among those serotypes contained in the vaccine. And that's what this slide shows. Notice that the scale on the left has gone from 120 cases per 100,000 at the top to about 90 cases per 100,000. So the majority of those cases we were seeing in children under the age of 5 were, in fact, vaccine serotypes. But now we see a 97 percent decline in the rate of invasive disease among children under the age of 5 with very narrow confidence intervals.

Even among older children, however, we saw a decline of 75 percent. And, again, this was

statistically significant.

Well another question might be what about those serotypes that are not contained in the vaccine themselves but are, in fact, related to the serotypes contained in the vaccine. And these would include things like 6A, 9A, 9N, etcetera.

This slide shows the rates of invasive disease caused by those vaccine related serotypes, excluding serotype 19A. And that will become evident in a minute why I've excluded that.

In children under the age of 5 we saw an 92 percent reduction in the incidence of invasive disease caused by these vaccine related serotypes. In older children we saw no statistically significant change.

What about non-vaccine serotypes, so those that are not in the vaccine and are not related to the vaccine? In children under the age of 5 we actually saw a 64 percent increase in the rates of invasive disease caused by non-vaccine serotypes. So this is replacement disease, and this is what we concerned might happen.

In children aged 5 to 17 we saw no statistically significant change and the rates were pretty much flat.

Well, remember a minute ago I told you that I was excluding serotypes 19A, and this is why. Serotype 19A has turned out to be the prominent replacement serotype among children under the age of 5. Between 1998 and 2004 we saw a 194 percent increase in the incidents of invasive disease caused by serotype 19A. I draw your attention, however, to the Y axis which peaks out at least in 2004 at about 8 cases per 100,000. So although in relative terms this is a substantial increase in the rate of serotype 19A disease compared to the huge decrease that we saw in overall disease and the even larger decrease that we saw in vaccine serotype disease, this is still a relative moderate increase.

Well, how did 19A become so common? I think this may have implications for future vaccine development. One hypothesis is that perhaps a new serotype 19A clone was introduced into the population, either from an area in the U.S. in which we're not

doing surveillance or perhaps from another country. Another hypothesis is that one or more of the 7-valent serotypes actually switched their capsules to become serotype 19A. So how can we try to address these two hypothesis?

This is where we get int our genetic testing using multilocus typing. This is a molecular typing method which determines the degree of genetic relatedness independent of the capsules serotype. It's based on the DNA sequences of seven "host keeping genes" which are relatively preserved in the pneumococcus over time. Each of these sequence types is assigned to a clonal complex or a family. Sometimes we call them clonal clusters.

So this pie chart on the left shows in 1999 among children under the age of 5 with serotype 19A invasive disease there were three different clonal clusters. The numbers clonal cluster 199, 81, 1665 are pretty arbitrary. The point of this pie chart is to show you that in 1999 there were really only three clonal clusters that accounted for all of the serotype 19A disease in young children.

If we were to think that perhaps a single clone came in and caused the increase in serotype 19A disease, what you would expect is that this pie chart would change by having just one additional section or color added to it. In fact, in 2003/2004 we've seen multiple new clonal clusters introduced into the serotype 19A population. Why did this happen?

Well, this same pie chart I've just moved over to the left side of this screen if the serotypes contained in the vaccine were switching their capsules to become serotype 19A, then you might think back in 1999 those serotypes might have been associated with other clonal clusters. And, in fact, that's exactly what we observe. Several of the new clonal clusters that are appearing in this serotype 19A disease used to be, in fact, associated with 70-valent conjugate vaccine types. So the really key message here is that previous vaccine serotype strains have essentially switched their capsules to become 19A strains.

Well, 19A is clearly a problem, but are there also other serotypes that are causing replacement disease in children, and that's what this

slide shows. Serotypes 3, 15, 22F, 33F and 35 all have increases in invasive disease among children under the age of 5. And for serotypes 3, 15 and 33F these findings have been confirmed by other investigators using other data sources.

So to summarize in children we've seen a dramatic reduction in the vaccine type invasive disease among children under the age of 5 with a substantial indirect effect among older children. There are some concerning increases in non-vaccine type disease, especially 19A. And there's substantial evidence now for capsular switching as a means of evading the vaccine induced immunity.

Now let's go on and talk about adults. This is a very similar slide to the first one I showed you in children, only this breaks down adults into four different age groups. Those 18 to 49 in the green line at the very bottom. Those 50 to 64 years of age in yellow. The 65 to 79 year olds are in pink. And the white line at the top represents adults 80 years of age and older.

So on the left hand side it should be

pretty obvious that the rates of disease vary considerably by age group. And notice that the population 80 years of age and older had a baseline rate in 1998 and '99 that was almost identical to the rate that we were seeing in children under the age of 5. However, over the subsequent years rates of disease in all of these age groups have declined substantially by about 20 to 40 percent and all of these changes are statistically significant.

So let's ask the same question again: Is this truly attributable to the vaccine? And one way we can look at that is by looking at changes in vaccine serotype disease.

These are the rates of disease in adults caused by the seven serotypes in the conjugate vaccine. And I think what's pretty striking is how similar all of these declines are. No matter which age group you look at you see anywhere between a 65 percent and a 75 percent reduction in invasive disease caused by these vaccine serotypes. These are all statistically significant changes, and obviously this has all hurt immunity.

One question that we often get a lot is how do you know that this is not attributable to either consistent or increased use of the polysaccharide vaccine? And one way to get at that question is to look at those serotypes that are contained in the polysaccharide vaccine but not in the 70-valent conjugate vaccine. And that's what this slide shows.

So these are those 16 serotypes. And you can see from 1998 through 2004 there was essentially no change in any of the age groups. If anything, there was a slight increase in the rates of these 16 serotype invasive disease cases among persons aged 50 to 64, which is shown in the yellow line.

So the key message here is that we do not think that these overall declines in invasive disease are related to polysaccharide vaccine. It's more likely that this is hurt immunity from the conjugate vaccine.

What about those vaccine related serotypes minus 19A? Remember that we saw substantial cross protection in children under the age of 5. Probably

no cross protection in children 5 years of age and older, and that's a similar thing that we're finding here. No statistically significant changes in the rates of vaccine related disease minus 19A in the adult population. So really no indirect cross protection has been observed in this population.

Getting back to this same serotypes 19A question is it happening in adults? And the answer is a pretty resounding yes. So between 1998 and 2004 we saw increases of anywhere between 77 percent and 2010 percent among the different age populations. All of these are statistically significant. Again, however, I need to draw your attention to the Y axis. Remember we were looking at rates of disease in the oldest age population of about 100 cases per 100,000. And now we're barely up to about eight cases per 100,000 in that same group. So statistically significant and relatively large increases in the instance of 19A disease, but in comparison to the reduction in vaccine serotype disease, it's still comparatively small.

Non-vaccine serotypes other than, this is actually including 19A and all of the other ones. It

seems that it's really statistically significant in the age population of 50 to 64 years of age. What about other non-vaccine serotypes? 19A is obviously statistically significant, but so in serotype 15, 33F and 35. So 19A is not the only story, but it is the majority of the replacement disease.

What about trends in syndromes and comorbid conditions? I'll refer you to the paper cited at the bottom here by Katherine Lexau that was published in *JAMA* a few weeks ago. She looked at a number of issues related to invasive disease in adults 50 years of age and older. The two that are highlighted here are syndromes and comorbid conditions. Essentially we observed that the incidents of meningitis was unchanged from 1998 to 2003, while bacteremia and invasive pneumonia cases decreased substantially over that time period.

In terms of comorbid conditions we saw that the proportion of case patients with HIV, diabetes, COPD and immunosuppressive therapy all increased. Now, this wasn't because the absolute rate of disease increased in those populations. It's that

the absolute rate of disease in the healthier populations decreased so much. So as a proportion of the total these individuals make up a larger proportion of our invasive disease cases.

We also saw that the proportion of case patients with at least one indication for the polysaccharide vaccine increased from about 62 percent to 72 percent.

Well I mentioned that HIV was one of those underlying disease syndromes that was becoming common in our case patients, and that's sort of what this slide is getting at. On the top half of this slide we're looking at rates of vaccine serotype disease among adults aged 18 to 64 of age with HIV or AIDS. In the lower half of the slide we're looking at vaccine serotype disease in adults 18 to 64 years of age without HIV or AIDS. So all of the other populations combined.

And what you see here is a fairly consistent decrease of about 60 percent in the rate of invasive disease in both of these populations. Now what about serotype replacement? In the HIV/AIDS

population we actually saw a 43 percent increase in the rate of non-vaccine type serotype disease, whereas we saw no statistically significant change in the rate of non-vaccine serotype disease among persons 18 to 64 without HIV or AIDS.

I would also point out that the rates here are remarkably different. The scale for HIV and AIDS goes up to about 700 cases per 100,000 whereas for the lower half of the slide it's about 10 cases.

What about actual changes in mortality? This slide is showing the mortality rate, actually both in children and in older adults expressed as deaths per 100,000 population. In the baseline period of 1998 and 1999 the mortality rate from vaccine serotype disease in children under the age of 5 was about 0.53 deaths per 100,000. And by 2004 that rate had declined by more than half to about .16.

For non-vaccine type disease the rate increased a little but, from about .08 deaths per 100,000 to .15. And overall, we still saw a substantial approximately 50 percent decline in the mortality rate for children.

Well, what happens if we look at the same thing in adults? We saw a very modest decline in the mortality rate for adults 65 years and older for vaccine type disease. A small increase for non-vaccine type disease. And the overall change is essentially zero. So sort of a disparity in the impact of the vaccine on mortality rates.

So to summarize the impact in adults, we saw a dramatic reduction in vaccine type disease among adults aged 18 and over. Some concerning increases in invasive disease caused by serotypes not in the vaccine. And the remaining cases are more likely to have comorbid conditions than several years ago.

To try to put all of this in perspective because I've been talking direct and indirect effects so much, this slide was published in the *Morbidity and Mortality Weekly Report* back in September. The bar on the left hand side of the screen shows the number of vaccine type invasive disease cases prevented by direct immunization of children. And it was approximately 9,000. But notice the bar on the right, which is the number of cases prevented among

individuals who are not targeted for the vaccine, so that would be older children and adults. The indirect effect of this vaccine has been roughly double that of the direct effect. I think many of us were hoping initially that we would see some indirect effects. I don't think any of us expected that it would be an effect of this magnitude.

What about expected serotype coverage in adults for different vaccine formulations? To reorient you, this is not a slide showing rates of invasive disease over time, but the proportion of all of our invasive cases that are caused by serotypes in different vaccine formulations. So at the bottom in the pink line that represents the 7 serotypes in the currently available conjugate vaccine. If a 9-valent vaccine were to become available for adults 18 years of age and older, and if that vaccine contained serotypes 1 and 5 in addition to the 7-valent serotypes, then we would see the yellow line. So this is a decline in a proportion of all invasive cases caused by those 9 serotypes over time.

The next line up, the green one,

represents an 11-valent product which would contain the same serotypes as the 9-valent product, plus serotypes 3 and 7F.

For the 13-valent product indicated by the white line, this would be the same as the 11-valent product except with 6A and 19A. We still see some declines, but not merely as much. And you can understand that now that we have pretty clear understanding of what's happening with serotype 19A and 6A.

And then finally at the top in the blue is the serotype coverage that we're seeing over time for the polysaccharide vaccine. Now you might ask, do these changes differ by age group? So now I'd like to just focus on calendar year 2004 and break it out by different age populations.

So in the 18 to 49 year old age group the pink bar represents the proportion of all invasive disease cases caused by the serotypes in the 7-valent conjugate vaccine. In 2004 that number was about 24 percent.

For a 9-valent product it was about 26

percent.

For an 11-valent vaccine, 35 percent. If you then add in serotypes 6A and 19A, we go up to about 54 percent.

And finally with the polysaccharide vaccine we're at about 84 percent.

These changes are pretty consistent across all of the age groups, although there are some minor variations within individual serotypes.

So in summary, serotype coverage ranges from about 22 to 85 percent depending on the vaccine and the age group. The 7 and 9-valent formulations are virtually equivalent in terms of their serotype coverage. And the 11, 13 and 23 valent vaccines would theoretically have incrementally more coverage from about 35 percent to about 85 percent.

Finally, what about opportunities for evaluation of new vaccines in adults. In the absence of a controlled trial what could we at CDC potentially do to help with this issue? One possibility is to do post-marketing surveillance for invasive disease. In fact, as long as we have the support to do it, we will

continue to do surveillance for invasive disease in all age groups. This, however, could also curve through other, perhaps, administrative systems such as Medicare. I think a fundamental concern about that is that there's generally no serotype information in those databases and, as Dr. Pratt indicated earlier, there are some issues around specificity.

Regardless of whether we look at ABC's data and administrative databases, we're also sort of looking at ecologic or temporal relationships. And that always makes it more difficult to assign causality despite everything we can do to look at individual serotypes or collections of serotypes.

Finally, we could do a case control study to evaluate the effective of conjugate vaccine in adults. This is a very reliable method that's been used for many years. There is some very recent experience in conducting such a study in children.

We could adjust for the routine use of polysaccharide vaccine. The major downside is that this would be quite expensive and very labor intensive.

So with that, I'd like to acknowledge all of the collaborators who participated in ABCs.

And thank you for your interest.

CHAIR OVERTURF: These three papers are open for questions and discussion. Are there questions or comments from the Committee members? Dr. Markovitz?

MEMBER MARKOVITZ: Just so I understand this rather key point. I know this was addressed, but I'd just like to hear a little bit more.

In terms of the opsonophagocytic assay there's no -- well, even though it's well validated in the lab, it's not validated yet as a measure of true immunity in patients, is that correct? Certainly not in the elderly. And it wasn't clear about what the story is with younger people. Could someone speak to that, since that seems to be a central issue here?

CHAIR OVERTURF: Please identify yourself,

DR. STEINER: Yes. This is Dr. Sandy Steiner, CDC.

And I believe you are correct. It hasn't been validated at that point. So those studies will

have to be put forward before you can use it that widely, I imagine.

MEMBER MARKOVITZ: Short of a very large clinical trial with that as a component of the trial, how do you think this could be validated? Is there a way to validate it in a more brief way or something like that.

DR. STEINER: The validation has been only for infants. And because we are discussing here is the adult vaccination, we have to concentrate on the adult population. And so it should be part of a clinical component trial of a large efficacy trial for adults. And the Finns included these as one of the components when they were trying to the titers measurements and trying to validate for titers. And they also salivary measurements and they looked at all the components too when they were trying to evaluate other endpoints that will be maybe protein candidates and everything like that.

So I think that in that respect you should consider it as part of the efficacy trials.

MEMBER MARKOVITZ: Perhaps you said this

and I missed it, but how good are the data correlating this assay with the protections seen in the infants? Was that part of the original trial or --

DR. STEINER: These was a subcomponent of the study, that's my understanding. That the black Northern California KaiserPermanente had its own endpoint and that only a subset of sera was evaluated for opsonophagocytosis. And that's what was published in the Judar paper where it was laid out available for a subcomponent of those sera that were posed those three for infants. And that's the only data that I have right now where there is a direct correlation.

There are data also from the clinical trials that the Finns have done. And they will also see correlation between opsonophagocytosis and ELISA and their protective levels. So all those trials are also available and in the literature.

If we put all the trials together, I think you will have enough information to put more weight to what opsonophagocytosis can do. That's a measure.

CHAIR OVERTURF: I think Dr. Self had a question.

MEMBER SELF: Yes. I'm interested in the serotype replacement question. First I thought the presentation of the data from the ABC was really terrific.

So you pointed out that the increases that you see up to 2004 are small in absolute magnitude. But I also couldn't help but have this feeling that the shape of that curve looked like the beginnings of an expediential kind of curve. And I'm thinking about the drop in all of the other vaccine related serotypes as creating this vacuum into which these 19A and perhaps others will be drawn.

Have you done any modeling work or would you hazard any prediction about over the next couple of years where those replacement serotypes are going to go?

DR. MOORE: The short is answer is no, we haven't. We would be very interested in doing that.

One thing that might help a little bit in that regard is to ask the question well why 19A? You know, why not something else? And I think the answer is a two part answer.

First of all, serotype 19A was already quite common before the 7-valent vaccine was introduced.

Secondly, it was already more likely to be antibiotic resistent than some other vaccine serotypes. Excuse me. Than some other non-vaccine serotypes. So in that sense 19A was sort of waiting at the door and it had this survival -- actually two survival advantages of being more likely to be antibiotic resistance and not already covered by the vaccine So in terms of looking forward, we could try to figure out what are the next serotypes that are waiting at the doorstep, so to speak.

DR. STEINER: I would like to add a comment to that, too. And it is regarding the thought that there will be some cross protection between -- if you include 19F in the vaccine that you will cross protected to 19A. And as you can see, there is evidence for the cross protection not to be present. And that is very important because in function when you're measuring the function and you look at type specific antibodies and only if it's type 19F as a

target will you be able to have good functional antibody activity.

So this adds information about functional antibody activity . We should not assume that we're going to have function that is cross protected. We have unpublished information for serotypes 15B and C which differ just by the -- of the polysaccharide and there is no cross protection of antibodies that are to 15B with functional antibody activity to 15C. And the only difference is the -- in the polysaccharide. The structure is exactly the same for the two.

CHAIR OVERTURF: Dr. Piantadosi?

DR. PIANTADOSI: Thank you.

I'd like to return just for a moment to this question about OPA and its role as a potential surrogate. I understand that it hasn't been validated in adults as a surrogate outcome. My question is if it were validated in adults for a particular type of vaccine, is there evidence that it would then also be valid as a surrogate for other types of vaccines?

DR. STEINER: You mean other conjugant vaccines or other vaccines outside of pneumococcus?

DR. PIANTADOSI: No, no. Other conjugates or other approaches to vaccines?

DR. STEINER: Like polysaccharide vaccines?

DR. PIANTADOSI: Yes, exactly.

DR. STEINER: Okay. When we have conjugate vaccination it's type specific antibodies being generated. So we can assume that protection will be applicable as a correlate of protection to the conjugate vaccines that are coming up. But when it is protein vaccines, you will not be able to use the same surrogate because we don't know all the mechanisms for function for each of the protein candidates that are being proposed.

Some proteins will mediate colonization, others may interfere with invasion. And the mechanisms by which they act or function may be totally different. Some of them may have opsonophagocytic activity and there are products that are being evaluated in that manner. But not all the products will have these opsonophagocytic activity. They may have a different functional antibody

measurement that is needed to be able to evaluate them.

CHAIR OVERTURF: Yes. Dr. Hetherington?

DR. HETHERINGTON: There are a number of questions that use of OPA raise with regard to use of the surrogate marker. We haven't talked about the pathophysiology of invasive pneumococcal disease. For infants it can be primarily a bacteremic disease and so it may make some sense to talk about serum titers and the use of utraphos. But what about for pneumonia? And it raises two questions.

Would studies utilizing pulmonary secretions be more appropriate. And what do we know about the transfer of antibody raised by vaccines across mucosal surfaces and its presence in pulmonary secretions?

DR. STEINER: Well, that's a very difficult question. And, yes, most of the studies that have been done has been assessing the serum antibodies.

Mucosal antibodies have been looked at by the Finnish group and they've looked at introitus

trials. And so there they could probably, if you review those, you will be able to see the correlation with protection. But the transportation of antibodies from the serum at the minimum levels that are needed in the mucosal surface to prevent, for example, colonization are also unknown. And there have been studies for hemophilus and influenza but for pneumococcal they haven't done.

For invasive disease like pneumonia as an endpoint it's even harder because we're having a hard time even defining pneumonia and the endpoints in the trials. The antibodies that will protect against pneumonia and with the background it's even harder to decide what will be the minimum level. Diagnoses of pneumonia and differentiating viral pneumonia and different etiologies of pneumonia, it's a major factor before we can even correlate to our laboratory correlated protection.

CHAIR OVERTURF: I'd like to ask Dr. Moore before he leaves, you mentioned the possibility of case control trials as a mechanism. What would be the possibility and the logistics of trying to combine a

case control trial with an evaluation with opsonophagocytic assays? It seems to me although it would be labor intensive, it might be one of the quickest ways to get some of this answered.

DR. MOORE: I think the biggest barrier would that our surveillance program is really based on -- it's an observational program. So patients are admitted to the hospital or seen in outpatient clinics. They're diagnosed with invasive pneumococcal disease. And then that case report and that isolate comes in days, weeks, months later depending on the situation. Because it is often very difficult to collect all of the information that's needed for the case report from.

So I think it's an issue of timeliness that you would want -- I presume you would want information about OPA early on at the time a person is diagnosed. And we typically do not collect serum, for example, at the time a person is admitted to the hospital and becomes a part of the surveillance program.

CHAIR OVERTURF: Do we know anything about

what happens to the OPA titer during acute pneumococcal disease? That was always an issue with the antibody studies because there was always a concern about decreases, actually, in antibody transiently?

DR. STEINER: Yes. Actually there is -- this probably has not been published either, but there is information regarding C-reactive protein. And in acute phase you will circulating C-reactive protein and that will effect opsonophagocytic titer. So when you do your absorptions of your sera you should dilute the sera to a higher initial dilatation to be able to dilute out the C-reactive protein and also measure the background of the C-reactive protein. I think this is very important to consider because it could enhance the opsonophagocytic activity -- so that is factor.

CHAIR OVERTURF: I think Dr. Farley was first.

MEMBER FARLEY: Mine is more based on the epidemiology. In some respects the initiation of the conjugate vaccine in infants has probably been more effective in preventing disease in adults than the

polysaccharide vaccine that's been around for a long time. And so I guess as we look at in the introduction or the process of introducing a conjugate vaccine in adults I'm wondering what we can add and how we should approach it. And another way is should we be looking at what the infant vaccine hasn't done and fill in the gaps in the adult vaccine. And that brings 19A right to the forefront and wondering if that should be fairly high priority for any conjugate vaccine in adults is to include that, or considering modifying a pediatric vaccine I guess would be another approach. But looking at the replacement or the prominent ones in a era of fairly good immunization of infants with this conjugate vaccine and looking at how we can work together in that system in the U.S., and I don't know if you have any comments on that.

DR. MOORE: Just that I would totally agree with Dr. Farley on that. I think it would be hard to envision how we would get a control on invasive disease in adults without something that would be effective against 19A since that seems to be the prominent one now. Obviously, including some of

those serotypes would be helpful as well.

CHAIR OVERTURF: Dr. Royal?

MEMBER ROYAL: First of all, I'd like to say that Dr. Steiner and others are to be commended on the work that they've done in development and validating the opsonophagocytic assay. But you would think that the more reasonable way to go would be instead of using an assay that uses HL60s, which aren't even mature neutrophils would be to use the patient's own neutrophils in a sort of modified ELISA assay.

DR. STEINER: Well, the only spot assay actually only looks at the B-cells that are producing the antibodies. So you will need to work with PAFI codes. And to truly have a good estimate of what are the cells that are producing the antibodies you should really have bone marrow samples or something like that, it's impossible to do. But if you're working with peripheral blood, you will only work with the PAFI codes.

If you wanted to use the own host phagocytic cells, there have been reports in the

literature that were cautioned a little bit about the function of the antibodies as people get older. And because the target population of the trials will have to be considered, the ages. Most of the trials that are being done or the studies that are being done are with really young elderly. People that are only 65 years or 70 or so. And really function starts going down as we get really, really old like 80, 90 years of age.

And with age there has also been the concern about the phagocytic function of the cells also not be as efficient in carrying out the function. So if you used the own host cells, you could take them but you'll need to have -- you'll have two parameters there. One, the function of the host at the time and the other one will be do they have antibodies circulating at the time, that will be need to observed out. And the other question that you have is the variability between the receptor's other phagocytic cells because there are differences in the receptors from donor to donor. Some of them are not significantly higher finity to the various

immunoglobulins that they complement as if you use one single standardized.

So if we want to compare across, it's probably easier to use for being able to compare one vaccine another vaccine in one population against another population across ages, a standardization is an absolutely necessity under those conditions.

CHAIR OVERTURF: Dr. LaRussa?

MEMBER LaRUSSA: Well, I'd like to expand on that answer a little bit. And I would argue that what you need are age match controls depending on the population you're looking at. Because you're going to come up with a level of antibody in a certain population, probably children or young adults, that correlates with the functional correlate, which is phagocytic activity. And then use that level of antibody as a target to get for the elderly population. And it may not work. You may need age match phagocytes in your study to see what the level of antibody you need in the elderly is.

DR. STEINER: Well, we have two components. One is the phagocytic cell, which is a

question on it sown. And the other one of the antibodies that are induced by the vaccine. So the major question is the function of the antibodies induced by the vaccine. The secondary question is the function of the phagocytic cell in the host that can vary by many, many parameters. Whatever, you know, compromising conditions they may have or by age.

CHAIR OVERTURF: Dr. Karron?

MEMBER LaRUSSA: But I guess if you're looking for a correlate of protection in the elderly, then you have to look at the second component, too. You can't just look at the antibody.

DR. MOORE: Exactly. That's my point.

DR. STEINER: I think the studies need to be designed to have that in mind as one of the items that needs to be looked at functioning in the host. Yes, I don't think that that can be ignored. It just has to be addressed, but maybe on a separate type of study.

CHAIR OVERTURF: Dr. Karron?

MEMBER KARRON: Actually, I have one question for Dr. Romaro and one for Dr. Moore. So my

question for Dr. Romaro is just to set back for a second. For the OPA assay in any system, in animals, in children, anywhere, has it ever been shown to correlate with protection against pneumonia.

DR. STEINER: No, we already answered this question.

MEMBER KARRON: No. I didn't think so, but I just wanted to be clear on that.

DR. STEINER: Yes.

MEMBER KARRON: And then my question for Dr. Moore is can you say something about serotypes and antibiotic resistance currently?

DR. MOORE: If I can have my slides back I can. I think it would be substantially easier to show that to you than to try to explain it.

Yes, I didn't think I would have time to discuss this during my talk so I brought these as extras.

This slide, it's a bar chart showing the most common current serotypes in adults in 2004. So this is all adults 18 years of age and over ordered in decreasing order of frequency. So 19A is most common

right now. 22F, 4, 3, 6A, etcetera.

The height of the bars themselves just represent the total number of cases we have caused by these serotypes.

The red portion of the bar represents the proportion of those serotypes that are not susceptible to pneumonia. So overall if you lump at all of these streams together, we're looking at about 20 percent non-susceptibility to penicillin. That gets back to this question of why 19A. It was already common and it was already antibiotic resistent before introduction of the vaccine. And we're seeing that those survival advantages are still holding it around.

The next one in line of terms of antibiotic resistance for penicillin would probably be 6A. But overall, these replacement serotypes appear to be less resistent than the initial ones.

Similar slide for erythromycin shows that the overall rate is very similar, about 18 percent. It's just that we see a little bit of resistance and lots of different serotypes instead of having all the resistance focused in one or two serotypes.

CHAIR OVERTURF: Dr. Self?

MEMBER SELF: I just want to close the loop a bit on the issue of study design. Case control studies can be just fine for estimating efficacy. But retrospective studies don't work very well, if at all, to assess correlates. The only possibility there is if you can do the assays on storage specimens and you have specimens that are prediagnostic. And none of that, I think from my understanding, is true in this case.

So if we're looking at evaluating a correlate, we are talking about prospective studies with specimens collected in some sort of regular fashion.

CHAIR OVERTURF: We need to break for lunch at this lunch. There will be ample time for more discussion for the afternoon.

So we'll break at this time and reconvene again promptly at 1:00.

(Whereupon, at 12:06 p.m. the meeting was adjourned, to reconvene this same day at 1:06 p.m.

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

1:06 p.m.

CHAIR OVERTURF: I'd like to call the afternoon session to order.

The first item on the agenda is the open public hearing. So I'll turn the meeting over to Christine.

SECRETARY WALSH: Good afternoon.

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

I have no received any requests at this time. Is there anyone in the room who would like to address the Committee at this time?

Dr. Overturf, I see no response. I turn the meeting back over to you.

CHAIR OVERTURF: The first presentation of the afternoon is Jan Poolman who will speak for GlaxoSmithKline.

PARTICIPANT: I'm sorry. I'm going to go

get him. He's upstairs. Just a minute.

(Whereupon, at 1:09 p.m. a recess until 1:11 p.m.)

DR. POOLMAN: Can I start?

Well, I apologize. But my paper said it was starting at half past 1:00, so I just busy with some other things. Sorry about it.

And thank you very much for invitation to speak on pneumococcal vaccines, which I'm doing with great pleasure.

At GSK Biologicals we have an intensive program pneumococcal vaccine development and we in late stages of development of a pediatric 10-valent conjugate vaccine. And we're also highly committed to develop an adult pneumococcal vaccine.

You may not know, but int he past GSK Biologicals, which was named differently in those days, developed a 17-valent vaccine when it was finally decided to stop and not continue to 23. And so all the experiences there and we are planning to build on our experience with pediatric conjugate development to develop adult vaccines, which are for

the shorter term, focusing on conjugate vaccines because of polysaccharide immunity, all well know, but also for the longer term we have programs on pneumococcal proteins, although the ideal scenario for a common antigen is obvious, but it's also obvious that is of a scientifically high risk because much less is known.

So, I will speak only about polysaccharides and conjugates in this presentation.

The situation with respect to polysaccharide immunization is that the current situation does give a substantial public health benefit by using the existing 23-valent polysaccharide vaccine, most by impacting on bacteremia, pneumococcal bacteremia.

It is somewhat contrasting but despite the substantial public health benefit the vaccine and its use have actually a marginal impact on the total burden of the disease, which if you add the two together would mean if you have a good program, you would have really an impressive impact on the burden of pneumococcal disease.

The reasons for the marginal impact are that the vaccine is only given once and also because the impact on pneumonia is shown to be low, although the actual level of protection against pneumonia is unknown.

So what are the reasons? And it has been demonstrated that the polysaccharide vaccine has intermediate efficacy against bacteremia. Most of these cases associated with what I call here about 50 percent efficacy are related to bacteremia. And like I mentioned, there's low efficacy against pneumonia. The precise level is unknown due to underpowering of the studies, but certainly also because of the difficulty to diagnose.

These data do suggest, and I'll come back to that later as well, in the pediatric context that it is easier to prevent bacteremia as compared to pneumonia.

One other major limitation of the existing situation is that the polysaccharide vaccine is only given once. There's no policy of revaccination. And this has a relationship with the uncertainty of

lowered responses upon revaccination, which we also call hyporesponsive. I call it uncertainty and I will mention one slide, and then I will stop talking about hyporesponsiveness and focus on the polysaccharide immune responses.

Here I put a quote from a not to long ago review on revaccination. And I think this is a fair statement. The limited data indicate that the responses upon the second dose are lower and the number of factors could play role, but definitely also the initial vaccination itself could play a role in these lowered responses.

So there is a need for further data here, particularly also looking at individuals that by themselves have a low response upon the first immunization, which is well known for any polysaccharide vaccine, even in pediatric, but also in adults with other polysaccharide vaccines, any polysaccharide vaccine does not completely immunize all subjects. There is a substantial portion, a minority but there is a substantial portion of individuals that respond poorly to a polysaccharide.

In general, with conjugate vaccines that poor response is resolved. This the data with other types of conjugate vaccines.

And it may very well be that revaccination of these already poorly responding individuals get even worse and those type of data are highly needed, but yet not yet known, but may play a major role in the limitations of the polysaccharide vaccine.

So now I go back to the polysaccharide immunity. Here is just an illustration of what I mentioned. There is about intermediate, I would call it 50 percent efficacy, against pneumococcal bacteremia. And this the review of Fedson and Musher in the *Standard Book on Vaccines* by Stanley Plotkin. And it's a summary of many studies. So it is intermediate, it's not complete.

This is what I mentioned in my introductory slide. This results into a relatively marginal impact on total burden of pneumococcal disease. So here I depict invasive disease, mostly bacteremia and pneumonia. It's a logarithmic scale, so it's a substantial difference. Much more pneumonia

than bacteremia. And this is what we currently do. We give one immunization at 65. That's what we understand from it works for about five years. And it works partially against bacteremia. So approximately 50 percent. So you take this piece of the burden of disease away while this all remains and it starts rising, as you can see here. So already way before 65. So this is a substantial public health benefit, but it is a marginal impact on the total burden of disease.

So initially it was expected with the earlier data with the polysaccharide vaccine that it would also be a significant impact on pneumonia. That was the expectation. And the expectations were driven by the early data in younger adults, which actually showed quite decent efficacy against pneumonia. And if you look through these publication, it's clearly pneumonia and it's also clearly non-bacteremic pneumonia.

There is an impact with the polysaccharide vaccine on adult pneumonia. And the expectations after these studies which led to the licensure of the

vaccine were high. Then after licensure the vaccine got used in the older age. And the results have been rather disappointing. Although, like I stated, the real extent is unknown because of the lack of the power of the studies that were done and because diagnostic tools were in general not sensitive enough.

So why is the impact of the polysaccharide vaccine different in young adults than elderly with relation to pneumonia. There are a couple of explanations. The antibody level is one. And certainly they could be lower, although the data in the literature did not suggest that there is a substantial difference. And I will show you some data also.

Then functional activity. There are some data out there, and I will show some additional data that confirmed these earlier data. And that could be an impact on functional activity.

Then also the mediator of functional activity, the primary mediator of the functional activity, the polymorphonuclear activity could be impacted as well. So if I may forget to say it

further on, I think with what we need to do is with the current existing assays that we use with cell lines, which are appropriate because they are robust and you can validate them and use them in high throughput, but these need to be validated in pilot studies and compared to -- from older adults, the elderly. Those kind of studies have not yet been done. In my mind these need to be done. Not to use them as a primary readout because that's not feasible, not practicable, not robust. These assays cannot be validated to the level needed. But to compare it to the assays with the cell line.

So antibody levels. You've seen this slide before. What we know from antibody levels and prevention of invasive disease, mainly bacteremia in infants, is that you need low levels of antibodies. And this was the result from a WHO meeting, but it was based on the KaiserPermanente efficacy data. You need low levels of antibodies to prevent pediatric bacteremia.

This is data that we have generated recently after polysaccharide vaccination in above 65

years old subjects. And using the highly specific assay that currently has become the standard for looking at polysaccharide human responses for the pneumococcus, which includes both intermission with polysaccharide and 22F polysaccharide. So finally after decades of some confusion of assays against pneumococcal polysaccharides we have an assay in hand that gives you the needed sensitivity and specificity which has been lacking for long.

By using this assay and using the similar principle was used for looking at what are thresholds linked to the observed efficacy in the elderly, what you see there is, what I mentioned, 50 percent efficacy against bacteremia mostly. And if you then look at 50 percent of subjects immunized what type of level they would achieve, it's about 5 micron per mil.

If you would look at the difference, the delta between the two, you come a little bit lower. In the range of 2 or 3 micron per mil that differentiates the best between the non-immunized and the immunized. But the bottom line message what I'm giving here, you need approximately ten times more antibodies in the

elderly as measured ELISA as compared to pediatric to prevent pneumococcal bacteremia. Now why is that?

And I come back in a conclusion slide yet right after this. And here is a great part of the explanation. Is we looked at immune responses in young adults, 18 to 25 mean age 30 years, and in elderly subjects above 65 mean age 72 immunized with the existing polysaccharide vaccine and we looked against the antibodies determined in ELISA as shown here. Not much difference. This is in line what has been shown in literature. There is significant differences.

If you would do an aggregate analysis there's approximately twofold difference. However, if you start looking at opsonophagocytic activity, the differences become huge, really dramatic, I would say. And you see most of them are significant. If we had used a little bit higher numbers, all of them would have been significant. And if you would do an aggregate analysis there is approximately five fold difference.

Now, I just mentioned that if you look to

the antibodies levels needed to prevent bacteremia there was about a ten fold difference. And here with opsonophagocytic activity between young adults and the elderly, you already find a five fold difference.

So if I go back to what I postulated here, certainly this is one of the key explanations of this question. It is a substantial of the answer.

So, like I mentioned, you need a much higher anti-polysaccharide antibody levels in the elderly to prevent bacteremia as compared to young children. And which can be explained in a number of ways, but certainly like I mentioned decreased opsonophagocytic antibody levels is a major player. And like I mentioned, we do need to look at PMN functionality in the elderly as compared to the cell line that we are using. It may give some additional explanation.

These are general also explanations that can play a role. Bacteremia in adults are mostly associated with pneumonia. They are not in children. And the responses to polysaccharides could in general be of less quality as compared to conjugates.

Although in young adults that doesn't seem to be really an outstanding observation.

So how does all this translate into the observation that, indeed, it is possible to prevent pneumococcal pneumonia. I've mostly talked about bacteremia now, but how does that translate into the observations made on pneumonia?

Like I showed earlier, the earlier trials in young adults did show that the polysaccharide had a clear impact on pneumonia in young adults, substantial impact. It has been shown that conjugate vaccines have had a substantial impact on pediatric pneumonia. It is possible. And the fact is that observations in the elderly are the exception. Those are the outlier. And I just gave I think a quite reasonable explanation which explains for a great proportion the reason why that is, why in the elderly do these existing vaccines prevent pneumonia so poorly.

And I've heard some discussion this morning on what is the mechanism of protection against pneumonia. And there was a suggestion that there's not much evidence of that -- opposite the facts

killing with PMNs play a role. I would like to turn that around. What other ways to explain it? These are intermuscular immunization leading to serum antibodies that do transudate. And if you look to pathohistological observations for pneumococcal pneumonia in the pre-antibiotic era, I think there is little doubt that only after the appearance of PMNs at the site of infection there was the start of signs of cure. And if you ask for 100 percent proof, definitive proof, that is difficult to give, never to give. But to put it on the other side that there is no evidence that what is the mechanism of protection here, I would say that is putting it in a situation which I think is highly unlikely. I really do think that antibodies that you induce by systemic immunization and in associating with polymorphonuclear sites are the primary mechanism of protection.

So this is just to illustrate the data that it is possible to prevent pneumonia. Here are the data with a 9-valent conjugate vaccine in South Africa and Gambia. It also shows a tendency that it is easier to prevent invasive disease, mostly

bacteremia, as compared to pneumonia. Its point estimates overlapping confidence intervals, but usually point estimates point you in the right direction. And it is in the same line what is observed in the elderly with polysaccharide vaccine.

And interestingly, the studies in the Gambia did not show a difference, again accepted widely overlapping confidence involved, but they did not show evidence of a difference in bacteremia or non-bacteremia pneumonia. I think also confirming the earlier trials in young adults with plain polysaccharide vaccine.

So I do think it's fair to state that it is easier to prevent bacteremia, but it is certainly possible to prevent pneumonia.

So how do we achieve the situation that the exceptional situation in the elderly where you have a poor impact on pneumonia can be improved? Well, one of the primary one is the anti-polysaccharide response needs to be made stronger, needs to improve because there is definitely a link between antibodies and protection. And you need

higher antibodies levels, more functional antibodies also to improve the situation on bacteremia because 50 percent prevention of bacteremia is not satisfactory, even if you have a 23-valent coverage, if you have 50 percent protection you have, let's say, an 11-valent vaccine. And that is certainly also needs, a high level of antibodies, against the polysaccharide for more morphonuclear antibodies to start to expect and to realize an impact on pneumonia in the elderly target population.

Higher antibody levels are needed. More functional antibodies are needed.

And also the broadening of the immunization just beyond the one immunization at 65 is needed. And in order to do that you need to be sure that revaccination is not leading to lower the responses. Like I said, we need more data to clarify the situation, but I do think it is very suggestive what has happened in a number of situations, not only with pneumococcal polysaccharides, but pneumococcal polysaccharides particularly in the ones that respond poorly in the first side will lead to even responses

after a second immunization.

We need more data, but it certainly needs to be resolved. And there indications that with conjugate vaccines this can lead to a better situation.

So I will end with a conclusion slide that what does this mean licensure of new vaccines. And which logically are, as you can hear from the presentation, are pneumococcal polysaccharide protein conjugate vaccines. And they do have the potential to improve.

I think my colleague from Wyeth, George Siber, will in his presentation demonstrate that it is possible to improve upon polysaccharide with conjugates. So in that context, what are licensure criteria for conjugate vaccines?

Immunonon-inferiority against the polysaccharide responses in the elderly or in similar age groups to my mind do need to lead to licensure acceptance for invasive disease or bacteremia. It's a similar approach we have been using for conjugate vaccines in pediatric. It's a similar approach we

have been using for conjugative vaccines in teenagers against meningococci. I see a little doubt in this area.

Then there is another interesting one which you could kind of hear during my presentation. What if you achieve with a new polysaccharide vaccine a conjugate vaccine? If you immunize elderly how would you feel about these data if you reach similar antibody levels, similar functional antibody activity as compared to what the existing polysaccharide vaccine has done in young adults, which certainly the current vaccine is not able to do? But what if your new vaccine would be able to do that and you know these data that exist with the polysaccharide vaccine in young adults?

In our view that is a clear steps towards expecting an impact on pneumococcal pneumonia. And that is also a clear step towards licensure for the pneumonia indication.

And then finally, the response after revaccination need to be non-inferior minimally, non-inferior to the response after the primary vaccination

so that there are no lowered responses. And in particular in these subjects that are fully responsive from the first start because those are the ones that are at highest risk.

So here I would like to stop my presentation. Thank you.

CHAIR OVERTURF: Dr. LaRussa?

MEMBER LaRUSSA: So two questions. One about the hyporesponsiveness after the second dose. What we've seen mostly is aggregate data. Have you separated out, is there a subject of adults who are hyporesponders and could you look at whether that's a function of their prior antibody titer? Maybe that's a subset that really can't respond to polysaccharide antigens.

DR. POOLMAN: It's a very good question. And we will be able to answer your question in I think about two years from now. What we have started to do, we have started to immunize a substantial sample size of the elderly above 65 with the plain polysaccharide. And with such a number that allows us to separate them into response categories and then do a follow-up

study a couple of years later by comparing the polysaccharide and then really have a clear view per serotypes, per response category of what is happening with the second dose of polysaccharide. But we also intend in that study to compare it to conjugate immunization.

So we have decided to generate this cohort to give specific answers for specific surrogates and for specific subgroups of poor, medium and high responders. It's an ongoing study.

MEMBER LaRUSSA: Okay. So the second question is in the slide that you showed with the responses in the elderly where you had the two curves, the pre-immunization and the post-immunization. And you said that what you did there was you looked at approximately 50 percent efficacy in the elderly, which was mostly you said in bacteremia. And looked at what the antibody titer at 50 percent would be.

Now, I know you don't have enough data to talk about efficacy against pneumonia. But couldn't you separate out the people who did and did not get pneumonia and look at what their antibody titers were,

and also look at them by the opsonic assay?

DR. POOLMAN: Someone may want to comment, but to my knowledge there is no data existing where we have baseline antibody levels that can specific serotypes linked to their susceptibility to specific serotypes pneumococcal pneumonia.

We are in an ongoing study with our college from Sweden to look in some cohorts he has. And it looks not unexpectedly that we need to generate and analyze the data further, that there is a specific deficiency in the anti-polysaccharide level or responsiveness in subjects that later developed that specific type serotypes pneumonia, which all makes sense. But we have rather limited data in that respect.

But I do strongly believe it's very specific event that the individual subjects that are poor response or have low levels and that become colonized, other ones that will develop type specific disease.

CHAIR OVERTURF: We have time for only one ore question.

DR. JACKSON: Okay. Well, you've made the case that the situation that we're contemplating about requirements for licensure of a new conjugate vaccine in adults is similar to situations that have been encountered in the past with meningococcal conjugate and with new Hib conjugates. But the key differences that in those cases the new vaccine had at least equal disease coverage as the old vaccine. And so if you prove non-inferiority, that meant that the new vaccine was likely, at least as good as the other one.

I mean, here we're talking 11 serotypes versus 23. So it would seem to me that even if you established non-inferiority for the 11 serotypes that the person would still be at higher risk of disease potentially by not having the total serotypes coverage. So I wondered if you could address that concern?

DR. POOLMAN: No, I fully agree with you. The non-inferiority criteria is a standard technical licensure criteria for which you have the guarantee that the serotypes in your new vaccine are at least equal to the same serotypes in the existing vaccine.

The next discussion is, and I hinted to that like functional antibody activity as well as hyporesponsiveness, that is a discussion that needs to develop what are the -- I hardly dare to call them, but it's what you would probably have to call them -- what the superiority criteria that you would need to see.

I do think that if you show significant higher antibody levels, that that does mean a stronger impact on the pneumococcal infection. And I do think that the absence of hyporesponsiveness if we demonstrate will allow you to come with revaccination programs which are currently not in place.

So the non-inferiority criteria is the minimum necessary to tell you that the serotypes in your new vaccine are at least equal.

DR. JACKSON: I would agree. But in the absence of a correlated protection I don't know what interpretation we can give to more. We can say at least equal, but if you say twice as much -- I don't know that we know what that means.

DR. POOLMAN: Like I said, that's a

discussion that needs to develop. But if you have clear superiority with respect with respect to functional activity and you have clear difference in superiority with respect to avoidance of hyporesponsiveness, I think that would have to be taken into a consideration, into account. And ideally, it would lead to a situation which I illustrated, that you would induce immune responses in the elderly that are comparable to the adult situation with the existing polysaccharide vaccine, which has clearly demonstrated a strongly impact in that age group.

CHAIR OVERTURF: We're going to have to continue on because we're going to be short of time at the other end.

So I'd like to call on Dr. Siber and thank Dr. Poolman for his presentation. Thank you.

DR. SIBER: Mr. Chairman, members of the Committee, my name is George Siber. I'm with Wyeth Life Vaccines. And I want to describe for you a proposal for how a pneumococcal vaccine for adults can be licensed.

What I'll show you, what I'll discuss, is

why there is a need for another pneumococcal vaccine in adults.

Secondly, the advantages of the conjugate pneumococcal vaccine for adults.

Third, the potential public health impact of such a conjugate vaccine in adults.

The proposed regulatory basis for licensing such a conjugate.

And finally, some discussion of the feasibility of performing clinical efficacy studies or lack of feasibility performing clinical efficacy studies with an adult conjugate vaccine.

So the first question is why do we need another pneumococcal vaccine for adults? Well, because there are limitations. They've already been discussed by the other speakers of the 23-valent polysaccharide vaccine. Antibody titers and efficacy appear to wane after 5 years. Effectiveness is very low in the immunocompromised patients. 23-valent polysaccharide induces hyporesponsiveness to either another dose of 23-valent polysaccharide vaccine given later or to a dose of conjugate vaccine, which I'll

show you shortly.

Revaccinations cause more severe adverse events. And multiple authors have described that. And therefore, as a general rule 23-valent is given only once which provides only a narrow window of protection during a prolonged period of risk beginning at about 50 years of age and increasing as we saw this morning progressively with advancing age.

And the second reason is because there remains a substantial burden of invasive pneumococcal disease in the U.S. These are 2004 rates here. With the impact of herd immunity already recognized from childhood -- and with 60 percent uptake approximately of polysaccharide vaccine and despite that as you see here in the older age groups there are still substantial rates of pneumococcal invasive disease and substantial number of deaths in the older age groups especially.

The second question is: What are the advantages of a pneumococcal conjugate vaccine for adults?

The benefits of a conjugate over

polysaccharides in this age group, and I'll show you the data to support the statements I'm going to make here, are the conjugate antibody responses are significantly better or non-inferior to 23-valent polysaccharide vaccine by both ELISA and by OPA measurements. Conjugate does not induce hyporesponsiveness to subsequent 23-valent polysaccharide vaccine or to a second dose of conjugate vaccine. Therefore, conjugate could be used to extend age range of protection against pneumococcal disease, for example down to 50 years of age and to provide long term protection by repeat dosing if needed.

So those statements are based on data that we have collected from a pilot study done with Prevnar, the 7-valent vaccine in Germany in elderly patients 70 years of age or older not previously immunized with a pneumococcal vaccine.

In year one patients were randomized to receive a 7-valent conjugate versus the 23-valent polysaccharide vaccine. Antibody measurements were done before and after immunization. A year later the

pneumococcal conjugate group was rerandomized to receive either a second dose of pneumococcal conjugate or the 23-valent polysaccharide. The polysaccharide group was not reramdonized; all of them received pneumococcal conjugate vaccine.

This shows you the immunogenicity by ELISA, geometric mean titers. In blue to the conjugate, in red to the polysaccharide. And the mean antibody concentration were significantly higher, about two fold to three fold after conjugate for all but one of the types, which is type 19F where the difference was not significant.

Now we've talked a lot about functional antibody concentrations and so shown here are the opsonic titers to the same seven types with Prevnar and 23-valent vaccine. Again, you see similarly that the opsonic antibody activity is higher, two to three fold, and because the higher variation of the assay that reaches significance for four, not six of the seven types.

So another question we were interested in asking is does prior polysaccharide effect the

response to pneumococcal conjugate vaccine? And to answer that question we looked at the lower group circled where pneumococcal conjugate was given after polysaccharide, one year after polysaccharide. And as a reference we looked at pneumococcal conjugate given initially without prior immunization.

And shown here in red is what happens to 7-valent responses after polysaccharide, one year after polysaccharide. And you can see that they are significantly lower for most types than when pneumococcal conjugate is given to a naive individual. This period of time is only one year. So immunogenesis cannot account for this. This is immunoresponsiveness which the conjugate vaccine was a probe to uncover, if you will, in this study design.

So Prevnar -- 7-valent vaccine blunts the response to subsequent Prevnar. So then the question is does Prevnar blunt the response to a second dose of Prevnar, and the answer is no it does not. And the green is Prevnar given as a booster dose, if you will, one year after the first dose versus in blue 7-valent given up front. And the responses are essentially the

same.

Another question is does giving pneumococcal conjugate effect the response to a subsequent dose of polysaccharide. And for this comparison we looked at polysaccharide given after pneumococcal conjugate in the circled group. And compared them to those who got polysaccharide up front. And what you see here in yellow are responses to polysaccharide after conjugate, and as you can see, they are generally somewhat higher than with 20 polysaccharide initially, but not significantly so with the size of this study. But certainly we don't see hyporesponsiveness induced by Prevnar for subsequent polysaccharide.

Now a question we wondered about is since there was only a one year interval between these immunizations whether this hyporesponsiveness would persist over a longer period of time. And what I'm showing you here are data from Lisa Jackson's study as yet unpublished but with her permission in which the interval between polysaccharide and conjugate was 5 years or more. And in her study individuals received

either conjugate in green or polysaccharide in red. And focusing on the conjugate responses you can see that they're actually remarkably similar to the responses we saw in a separate study, different country but similarly aged patients suggesting that probably longer intervals won't mitigate the hyporesponsiveness that we see after 23-valent polysaccharide vaccine.

And this just to answer a question, actually, that was raised earlier. With repeated doses of polysaccharide vaccine, this shows you the responses. The first two points here are the response to the first dose of polysaccharide. Then the next point is a year out. The fourth point is three to seven years out. And then a second dose of polysaccharide is given and you see the responses of that. And it's clear that for four of the six types that were examined there is a significant reduction in the ability to respond with the second dose of a polysaccharide which has been termed "hyporesponsiveness."

So the data I've shown you on

immunogenicity I think support the following:

First of all, that Prevnar conjugate can be used repeatedly without inducing hyporesponsiveness in the elderly.

Second of all, that 23-valent polysaccharide can be given after pneumococcal conjugate vaccine without hyporesponsiveness.

And if both vaccines are used to maximize coverage, conjugate should be used first.

The third question is what is the potential public health impact of pneumococcal conjugate vaccine for adults? Now, you need to make a series of assumptions, and in your briefing package these assumptions are outlined in a lot more detail than I will here. But to summarize the assumptions we made were that serotype coverage based on the 2003 incidence of disease in the U.S., so it takes into account to a large extent the herd immunity effect of Prevnar, is 75 percent currently for 23-valent polysaccharide vaccine and 56 percent for the proposed 13-valent conjugate vaccine.

Invasive pneumococcal disease rates are,

again in the briefing package, but they do reflect the herd immunity effect of Prevnar. But what was done was to back out, if you will, the effect of the use of 23-valent polysaccharide using assumptions that were in a paper published by Fry, et.al. So they actually adjust upwards slightly assuming 23-valent is not being used.

We assumed then that the efficacy for a pneumococcal polysaccharide vaccine would be 88 percent for five years. That's based on the Shapiro study. And thereafter declining to essentially zero percent by about 15 years.

In contrast we assumed that for 13-valent vaccine efficacy would be the same for polysaccharide but could be maintained at the similar level throughout the risk period.

We assumed neither vaccine would be efficacious for the immunocompromised patients. And the vaccine uptake, the assumption was the current level of update that we have achieved with 23-valent, which is 60 percent in over 65 years old, 43 percent in high risk groups under 65 and zero percent in

healthy under 65. In contrast 13-valent conjugate uptake would be 60 percent from 50 years onwards.

Using those assumptions one can then estimate of numbers of cases prevented and in parenthesis deaths prevented by these vaccines. The 23-valent vaccine shows a low level of prevention from using it in high risk individual under 65 and then a peak of protection assuming everyone gets immunized. And then weaning prevention over time. And so the net effect of all of that is calculated to be under 3,000 cases prevented and a little under 500 deaths prevented overall per year.

If one were to use a 13-valent alone and assumed with potentially repeat immunization one maintains protection at 88 percent throughout the high risk period. One would prevent, despite the somewhat lower coverage of 13-valent, almost twice as much, 86 percent more cases of disease and deaths.

Now it's possible, as we mentioned, to give the 13-valent first followed by polysaccharide and get the advantage of the additional serotype coverage that way. And the additional cases prevented

by doing that are 566 with about 93 deaths. And the total number of cases prevented, as indicated, is over 6,000 and almost a 1,000 deaths.

Now these estimates are really quite conservative in terms of what the public health impact would because we don't assume any IPD efficacy despite the fact, as I've shown you, that we have higher ELISA and OPA antibody responses. We also don't assume any protection for the immunocompromised groups although there are data. In HIV positive patients, for example, the responses to conjugate are significantly better than they are to the polysaccharide as well as in other high risk groups such as renal dialysis patients, individuals who have been shown to be hyporesponsive to polysaccharide subsequently immunized with conjugate that respond and so forth.

It also assumes no efficacy for pneumonia even, as I'll show you in a moment, the OPA antibody after pneumococcal conjugate in the elderly is actually similar to OPA antibodies after three doses in infants.

I want to emphasize here that we are not

making the case nor or we requesting that there been an indication for pneumonia. That may be a benefit of a vaccine, but we don't believe that we can demonstrate that prior to licensure. Rather, we're going to make the case that we bridge to polysaccharide, which we know to be effective in the elderly population and in the adults. Okay.

Now the fourth question is are serologic studies adequate to demonstrate efficacy of adult pneumococcal conjugate vaccine? Historically there have been two approaches used for licensing polysaccharide based vaccines, whether polysaccharides or conjugates. First of all, when there is no vaccine to prevent the disease in the particular age group, an efficacy trial is required if feasible. And examples of this from the past are the 14-valent polysaccharide vaccine, the Group A and C meningococcal vaccine, the Hib polysaccharide vaccine in toddlers, which we licensed based on the Finnish efficacy trial, the Hib conjugate vaccine in infant based on Navaho and Kaiser trials and the pneumococcal conjugate vaccine in infants based on Kaiser. However, when there is

already a licensed vaccine to prevent disease in particular age group, immunogenicity comparison has been acceptable to extend the coverage to other serotypes or to improve the level of immunogenicity by switching to conjugate from polysaccharides

And examples of that are the 23-valent pneumococcal polysaccharide after 14 extending serotype coverage, the 4-valent meningococcal pneumococcal after 2-valent, again to extend serotype coverage, the Hib conjugate vaccine after Hib polysaccharide vaccine in toddlers to achieve better immunogenicity. There was no efficacy trial done for that in toddlers. And very recently, as was mentioned earlier, the 4-valent meningococcal conjugate vaccine Menactra after 4-valent polysaccharide vaccine based purely on serology, no efficacy trials.

So the proposal for licensing adult conjugate then is based on the regulatory precedents that the efficacy of a pneumococcal conjugate for adults can be proven by showing a serologic non-inferiority to the shared serotypes in the licensed 23-valent polysaccharide vaccine based on OPA assays.

Secondly, that there be lack of hyporesponsiveness to second dose of conjugate vaccine which will enable repeat doses if needed to maintain protection.

And thirdly, that there be a lack of hyporesponsiveness to 23-valent polysaccharide vaccine given subsequently, which would enable extending serotypes coverage in high risk groups if so desired by advisory committees.

Now, the scientific basis for serologic studies showing efficacy of this vaccine is as follows:

First of all we know that the efficacy of the 23-valent vaccine is established and we know that the only antigen in that vaccine that could provide protection is the capsular polysaccharide. So the polysaccharide is a protective antigen. There's no question about that.

Second of all we know that antibody is the protective mechanism against invasive disease. There's no question about that either. Passive immunoglobulin therapy protects against pneumococcal

invasive disease.

Thirdly we know that opsonophagocytosis is the protective mechanism. At the risk of sound dogmatic, there is no alternative mechanism whereby antibody can protect that's known.

Fourth, induction of opsonophagocytic activity is believed to correlate with clinical efficacy and is proposed as a primary basis for comparing adult vaccines. Now, I'll show you a little bit more information from which we could infer that that's a reasonable hypothesis. I think absolute proof, it would be hard to come by.

And five, antibody binding assays such as ELISAs can be used as surrogates when they correlate highly with OPAs, as is the case in infants where the correlations are very high. Our experience, like that of others who have spoken earlier, that is in the elderly that correlation isn't very high, it's rather low. And therefore OPA measurements are probably more appropriate as a direct measure.

Now just to review what others have mentioned before is that there is very substantial

evidence, convincing evidence that the polysaccharide vaccine is efficacious for invasive disease. There is much less convincing evidence, as others have also commented, that it's efficacious for pneumonia in the elderly, and therefore when we bridge to polysaccharide we can only expect to bridge to it for an invasive disease indication.

Now, why is OPA the appropriate laboratory measurement to use in adults? Well, we know that OPA in infants is very high and efficacy of this conjugate vaccine in infants was also very high. And so the high OPAs appeared to correlate with high efficacy.

Of particular interest, though, is one of the types, type 109F, has lower OPA in infants than the other six types. And although the efficacy of Prevnar for 19F is quite high, it is lower for otitis media and for inhibition of 19F colonization. And it seems to relate to the low OPA. And let me show you the data on which those statements are based.

Shown here at the ELISA titers, geometric means after three doses of Prevnar at seven months of age in infants on the left column and then the OPA

titers on the right.

And you can 19F stands out as having a low OPA titer relative to all the other types. And so the question is does that correlate with anything clinically. And the answer, it does seem to.

Now for invasive pneumococcal disease it's not very dramatic, although it's true that both in the Kaiser study and in the ABC case controlled surveillance that was done more recently, the 19F point estimate of efficacy is the lowest of all the seven types, 85 percent and 81 percent respectively.

Otitis media where the demand on having antibody is probably greater shows this lower protective activity better. And here 19F has only 25 percent efficacy. Much lower than the other six types. And for colonization as well, and this is just data in Israel, 21 percent. In fact, it's quite striking looking at the data how well colonization inhabitation correlates with otitis media efficacy.

OPA also explains what has been to many of us a conundrum, which is why do the elderly who have reasonably good binding to antibody activity have such

a high risk of disease. Specifically elderly adults have similar ELISA antibody levels even prior to immunizations as infant do after Prevnar. And yet they are at very high risk of invasive pneumococcal disease. The explanation, as you already heard also from Jan Poolman, is that pneumococcal antibodies in the elderly have lower opsonic function relative to infant antibody. And I will show you some more data on that.

So first of all on the point of what the elderly ELISA antibody concentrations are even prior to immunization, shown on the right here are elderly unimmunization individuals, geometric concentrations, all around a microgram. And then in infants after three doses. They are higher, but not a lot higher. And if one used the infant derived population based estimate of protection of .35, the WHO Committee has suggested, most of the elderly should be protected and apparently they are not.

If you now look at the OPA titers in red you see the dramatic difference in OPAs between the elderly and the infants. And we propose that this

difference is what predicts the fact that the elderly without immunization are at risk.

So the quality of the antibody in the elderly is much less than in infants. However, after a single dose of Prevnar in the elderly there is an increase in OPA antibody titers to levels similar to that in infants after three doses. And that increase involves both quality improvement as well as absolute concentration improvement.

Shown in black is the ELISA antibody concentration in the elderly after immunization. And what you can see is that they're actually higher than in infants by substantial amounts in many cases. And the OPA antibody now is similar to infants, albeit the quality, the functional quality of OPA activity per microgram of antibody in the elderly is lower. But the net OPA is similar.

So, again, the proposed licensing criteria for adult pneumococcal conjugate then are to demonstrate non-inferiority of the immune response of the shared serotypes in the 13-valent conjugate and 23-valent polysaccharide with the primary comparison

being based on OPA.

To demonstrate no hyporesponsiveness to a second dose of 13-valent, and this will support repeat dosing of the 13-valent for long term protection if that's needed.

And to demonstrate no hyporesponsiveness to subsequent dose of 12-valent. And this would support a recommendation to use 23-valent polysaccharide to extend serotype coverage in high risk groups, if desired.

So the final question is whether an efficacy trial is feasible for invasive pneumococcal disease or for community acquired pneumonia. And I think, as speakers before me have mentioned, there are a number of constraints on performing pneumococcal conjugate vaccine efficacy trials in adults for CAP or IPD. A placebo controlled trial is necessary if we are to assess in any true sense the efficacy of 13-valent vaccine. Placebo is not possible in high risk adults who are currently recommended to receive the 23-valent vaccine. And that means over 65 and those under 65 with the high risk conditions for which the

polysaccharide is indicated.

Therefore, only healthy healthy less than 65 year olds can be studied. In this age group 72 percent of all invasive disease occurs in the high risk portion, which would have polysaccharide. So we're left with IPD rates in the healthy less than 65 year olds that will be much lower than those for the entire age group. And those have been generally used for the calculations we've heard so far. They will be lower in the healthy group.

So as a result studies of IPD or CAP in those groups would require absolutely enormous sample sizes in excess of 100,000.limb for adequate power. A variety of alternative designs have been discussed such as using a combination of 13-valent polysaccharide versus 23-valent alone, and then being able to do it in high risk groups. But if you use IPD as the outcome with a somewhat efficacious 23-valent vaccine, those study sizes would be even larger than the ones we're calculated.

So post-marketing effectiveness studies are really the only feasible way, in our opinion, to

assess the impact of 13-valent vaccine on IPD and possibly on CAP. And we've seen very elegant work from the ABC system described this morning of how effective our ability is to look at IPD rates and incidents over time.

So but just to go through the exercise, and I think Doug Pratt did so this morning as well, with a few I think more realistic assumptions about rates, what would the sample size be for IPD in 50 to 64 year old healthy adults? And our assumption of an incidence rate of vaccine type disease, vaccine type disease is 25 per 100,000 or as a high rate, and that's be a very high rate, 15 per 100,000 as an intermediate rate and 7.5. per 100,000 as a low rate.

And we should note that the CDC estimates Prevnar in healthy 50 to 64 year olds are 9.9 per 100,000 rate. So I think now with herd immune effects and only vaccine coverage of 56 percent, the 7.5 is probably the realistic rate we could expect in this study population for IPD. We assume 56 percent IPD coverage by 13-valent. We try vaccine efficacies, true efficacies of 70, 80 and 90 percent; 90 percent

power. Lower 95 percent confidence intervals greater than 30 percent and a realistic trial length of a total of three years; one year to enroll, two years to follow-up, a mean follow-up time of 22 years.

So with those assumptions this shows you the numbers of patients per limb that would be required to achieve an adequately powered trial. Now we can dismiss the 25 per 100,000 estimate as being unrealistically high for a healthy 50 to 64 year olds. So look at the 15 and the 72, and I think 90 percent efficacy is unrealistically high as an expected benchmark in the elderly as well.

So the red figures are the numbers that we ended up for possible trial sizes. And we believe that in healthy 50 to 64 year olds they will not be possible to do trials of that size.

Without going into figures, but there are a variety of major issues with CAP outcomes. Again, we can ethically only say healthy less than 65 year olds here, and probably much of the CAP incidence in the 50 to 65 year old group that is talked about is in high risk individuals. So the CAP risk will be low and

sample sizes will be extremely large.

We don't really know the proportion of CAP that is due to pneumococcus, and so that makes estimating sample sizes uncertain and increases the risk.

The etiologic diagnosis of pneumonia would enable a smaller sample size. There's no question about that. But unfortunately, there is no validated method available today to do that. And if your method picks up cases that are false/positives in your control group, the sample sizes would be driven even higher. And for us, the lack of a validated outcome is a show stopped for vaccine type CAP efficacy trials.

And finally, as I mentioned before, I think our ability to enroll very large numbers of healthy low risk individuals into such trials I think would be limited.

So my conclusions are that 13-valent pneumococcal conjugate vaccine has the potential of a significant public health impact because it can extend the duration of protection throughout the high risk period.

The 23-valent polysaccharide vaccine may be given after the 13-valent pneumococcal conjugate vaccine to expand serotype protection in the high risk groups.

Efficacy of a conjugate vaccine in adults can be proven by showing non-inferiority of the immune response to the licensed polysaccharide vaccine for the serotypes that are in the conjugate. Placebo controlled efficacy trials in the adult population are not feasible due to ethical considerations and size.

And effectiveness against IPD can be confirmed in post-marketing studies.

Thank you.

CHAIR OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: Yes. Because you guys make Prevnar, I hope you're the right person to ask this question. A number of us were talking about this over lunch. And what I haven't seen yet and it didn't come up in your data, obviously with adults we really don't know, but even with the kids in the initial trials you did that showed that Prevnar was successful, were you able to actually look at kids who

did get pneumococcal disease and show that they had lower opsonophagocytic responses? Are there any data actually to really address whether there's a correlation here? Because like what you showed here, pointing to that one serotype where you had lower levels and was somewhat less efficacious, it appeared that the levels were considerably lower but yet the efficacy was only marginally less. So do you actually have data from that original trial that could help us to at least understand whether this test is useful in some setting in a more definitive way?

DR. SIBER: Are you asking about data prior to disease?

MEMBER MARKOVITZ: Yes.

DR. SIBER: We do not have such data with pneumococcal disease. The problem with that is that you have to bleed every child in a very large efficacy trial, and that has not been done.

There are some examples where such sera are available, but they're anecdotal. One of the best ones is from the Hib efficacy trial conducted on a Navaho reservation where they did bleed every child, I

believe, and they had a serum on a child who subsequently became ill with Hib disease. And what you typically find in this setting, and there's some examples, I actually reviewed this a few years ago, is that the antibody levels of those who end up getting sick are now lower. They fall in the same range of those who are protected.

And the notion that you can simplistically look at somebody's antibody level individually at a particular time and expect to predict individual based protection is false. Can't do that. You can do population based protection estimates. We cannot reliability on an individual basis predict protection.

MEMBER MARKOVITZ: But what about looking at the kids who got -- but I guess perhaps I didn't ask that question properly. What I really want to know, and apparently there are no data but correct me if I'm wrong, has there been an analysis of the levels of those antibodies overall in kids who did get sick versus those who didn't get sick? I assume not because you didn't bleed everybody.

DR. SIBER: Right.

MEMBER MARKOVITZ: So the answer really is there are no data to directly address this question?

DR. SIBER: Not prior to illness.

MEMBER MARKOVITZ: And did you have data after the illness, though?

DR. SIBER: No. I don't think so. I'm not aware. Maybe there are such data. I'm not aware that people have collected systematically data of breakthrough cases to look at the antibody concentrations with the pneumococcal vaccine.

CHAIR OVERTURF: At the microphone. Just identify yourself.

DR. POOLMAN: Jan Poolman from GlaxoSmithKline.

And we actually did that in the situation of a no otitus efficacy study where the number of children involved are lower, so you can have your prebleeds. We still have to publish. But your children that came down with otitus media later on, for the few serotypes where we had sufficient cases in each case for each serotypes there were about three or four serotypes, has substantially lower

opsonophagocytic antibody levels.

DR. STEINER: Sandy Steiner from CDC. We also have a comment on that.

The Navaho trial that was done with Kate O'Brien there was one child that we happened to have serum also before, throughout the bleeds. One of them was vaccine failure. I'm trying to remember the serotype, but I think it was 19F. And -- or 14 actually -- was 14 serotype. And we'd like at the titers, the opsonophagocytic titers and they were reduced by the single serotype killing assay. When other assays were looked at actually, it was not reduced. But for the killing assay it was significantly reduced of opsonophagocytic titer.

And it also had lower avidity. It happened to be the child that had the lowest avidity of all the controls that were run along with this child.

This study still has not been published and we're working on the publication with Kate O'Brien, so it's very confidential.

MEMBER MARKOVITZ: I'm sorry. Are you

differentiating between phagocytosis and --

DR. STEINER: But we need to know these.

MEMBER MARKOVITZ: Thank you. We'll keep it quiet then.

DR. STEINER: Yes.

MEMBER MARKOVITZ: May I ask, did I understand right, are you differentiating though between phagocytosis and killing are you using those synonymously.

DR. STEINER: No. Measuring of phagocytosis by the killing assay. Measuring. Yes.

CHAIR OVERTURF: Dr. Steinhoff, you had a question?

DR. STEINHOFF: Well I'm going to change the subject. I don't know if there's another one about OPA. As long as you call on me later.

CHAIR OVERTURF: Dr. Hetherington then?

DR. HETHERINGTON: This may be short.

Dr. Siber, if we agree that older adults have a deficiency in OPA, do you have any sense as to where that deficiency lies? For instance, is it the sub blast distribution of the antibody response

knowing IGG4, for instance, is opsonic?

DR. SIBER: I would be really speculating about how it happens. I think there's some hypothesis you can generate based on what we know. If you believe that polysaccharides induce hyporesponsive, we showed you some data that they may. Over time we see the pneumococcal polysaccharides many times. If each time polysaccharides drive your B-cells to make antibody without replenishing memory cells, you can imagine over time that the memory cells of your best clones become less and less and you start recruiting not so good clones, and those may have less opsonic function. That's a hypothesis.

DR. POOLMAN: Once more, sorry. Jan Poolman, GlaxoSmithKline.

And there are two very recent publications in effect immunity, from Julie Westeringsteam. She shows that in the elderly the variable regions of both the heavy chains and the light chains are substantially different as compared to the adults, which must translate into functionality, like it clearly does.

DR. SIBER: It's very consistent with the hypothesis I just mentioned.

CHAIR OVERTURF: Dr. Steinhoff?

DR. STEINHOFF: It's interesting to hear this because I was going to raise the issue, George, that you very early on showed the age distribution of disease which has a U shaped curve increasing in adulthood. And I was not aware of this data that the nature of the antibody changes in the elderly. Because the level doesn't. The antibody titers stay pretty much the same for age 20 to age 50 or 60. So the question is is it the antibody that changes, and perhaps it does, but I also wondered if the cellular function doesn't change? And that would account for titers that are about the same but function that is much less. Because the other limb of the OPA is the white cell function. And maybe they both change.

DR. SIBER: Well, I think you're right that the quality of the antibody very clearly changes. And I think our best measure of that is the opsonic functions falling.

You know, I can't speak to the white cell

function in the elderly. I don't think we have data one way or the other on that to my knowledge.

CHAIR OVERTURF: What about affinity specifically, which is another measure of antibody function? Has that been looked at?

DR. SIBER: Dr. Steiner, you may have data on affinity in the elderly. I don't think we do.

DR. STEINER: Yes. We have the publication from 1999 and that was on the elderly where there was very low -- measurements. It was affinity, it was a -- measurement. And it was very low if you measure it in molarity for -- compared to the young adults. It was in the range of less than .1 more. And for the young adults it was in the range of 1.1 to 1.3. So it's like a ten fold difference. And it also correlated with function. Those that had the low of the antibodies did not have function and those with the higher had high function.

That's the same study that was done in adults by Lucas, Alex Lucas. And even though they were not elderly, it confirmed the studies that we had done on the same year.

One more question. There was a question regarding the B-cells. And in 2005 there was a publication that just got published in infection and *Immunity and Aging* is the journal. And with Dr. Westerings group. And we collaborated.

We saw that also the numbers of these cells that are present in the elderly are lower in the very elderly in comparison to the normal young adults. So the numbers of cells, not only the clones maybe lower that are present, that's something that we should also consider looking into.

CHAIR OVERTURF: I think Dr. LaRussa was first here.

MEMBER LaRUSSA: Just to comment and then a question. In a number of the examples that you cited where we were able to approve a vaccine based on inferiority to something that was already there, I just want to remind people that in two of the examples we were essentially adding on to what was already there covering more serotypes. So you could argue that even if the additional serotypes didn't work, you weren't subtracting anything.

In the case of hemophilus we knew what the correlates of protection were. So that really doesn't count. And I guess the one example where you could say we really did add a vaccine on the basis of non-inferiority was the meninga example. So that's just a comment.

I want to go back to one of the scenarios that you dismissed for efficacy. And what I would argue is that in the age group over 65 you really could revisit the scenario of giving conjugate first and polysaccharide second and studying efficacy against community acquire pneumonia. Because we don't really believe that the polysaccharide works that well against pneumonia. And although it would be a large trial, it really would answer the question of efficacy in the age group where we really need that question answered.

So I wouldn't dismiss that. I would think about that more seriously.

CHAIR OVERTURF: Dr. Karron?

MEMBER KARRON: Partly as a follow-up comment to that, I think I had a question about,

George, you're saying that a placebo controlled trial would be necessary to test efficacy, particularly thinking specifically about CAP since we don't really think in people over 65 there's appreciable efficacy of the polysaccharide vaccine. So whether you have the kind of scenario that Phil was suggesting of sequential immunization or whether you had a head-to-head comparison, would that be possible?

And the second question I had for you is what about the issue of doing an effectiveness study for CAP? I mean, would that be feasible? I understand that definitive diagnoses is difficult, but is that feasible?

DR. SIBER: Well, I think the numbers would be enormous, but I think beyond the numbers, even in the high risk population over 65 the difficulties we've encountered with pneumonia outcome are best illustrated maybe by the debates we've had about even the pneumonia efficacy of this vaccine in infants. And I would remind the group that we have not been able to agree amongst the regulatory agencies, investigators or WHO on a definition that we

all agree is pneumonia. And that's in infants, where it's relatively straightforward, in my opinion, compared to older people with their background of x-ray issues.

And as we talked about earlier, the outcomes with regard to microbiological documentation are problematic. We simply don't have a validated way to make a pneumococcal diagnoses.

So we are left with a situation we're very uncertain about how we could agree on an outcome for a pneumonia study in any kind of study. And on top of that we have the issue, I mentioned that the huge sample size required even with the current rates of CAP, if you accept those as real and those come, I believe, primarily from diagnoses put into charts by doctors.

So I think you're left with a tremendous amount of uncertainty in designing such a trial, and a tremendous sample size to do it.

Also, all of you are reasoning that pneumococcal polysaccharide does nothing to CAP. I think there's been a lot of debate on that issue. It

may do something, it may not do something. The power of most studies have not been adequate, really, to address the issue. So if we powered a study at the size we're talking about, hundreds of thousands of individuals, there'll be this uncertainty about what the pneumococcal polysaccharide control did. And so you're left with some uncertainty there for what conjugate efficacy would be.

CHAIR OVERTURF: Dr. Jackson?

DR. JACKSON: Yes. I was shifting gears a little bit. I was looking at your model demonstrating the estimated public health benefit of a conjugate program versus current status of using the polysaccharide. And most of the relative benefit of the conjugate vaccine program occurs at prevention of cases in pretty the very elderly, 75 and 80 or 80 and over. And I think although certainly tolerance has been a concern, but part of the reason that we don't have routine revaccine may also be because of concern that there's a lack of primary immune response or a lack of effective immune response in persons in their late 70s, 80s and older to the polysaccharide vaccine.

So it does raise one question, which is what's the mean of non-inferiority in an age group in which perhaps we're not so sure what we've currently got is terribly effective.

And the second is what would you propose to do to ensure or to try to try to estimate of the conjugate vaccine in this older end of the age spectrum where most of the disease is occurring?

DR. SIBER: Well, I think non-inferiority is what we would formally propose, and that's a really a regulatory convention to look for non-inferiority. That's a requirement. And my opinion is the minimum requirement. And as I've shown you, we are actually seeing a significantly higher responses with conjugate versus polysaccharide. And we assess the 13-valent properly in this setting we would hope to see the same similar higher response.

In terms of showing the impact, I am very confident that the ABC system, which really looks at disease in all age groups, will provide excellent data but it requires the vaccine to be introduced and used. But we will find out what the impact is over time

through ABC. And that will be the best data that we can hope to expect.

CHAIR OVERTURF: Last question. Dr. Farley?

MEMBER FARLEY: I think many of us are sort of grasping on to trying to get some clinical outcome as part of this measurement. And I'm curious to hear your comments on what you think the role of colonization studies might be assessing this in adults, realizing that the carriage rates are going to be lower in adults? But do you think that would have any benefit or play a role in assessing pre-release of this vaccine?

DR. SIBER: No. I think it would be very interesting to try to show an effect on colonization in adults. As you point out, the big problem that in the absence of children in the household, the studies of colonization are from one to five to six percent. Then when you consider what proportion of those will be vaccine serotypes, that also will be an extremely difficult undertaking to do that. It's something we would like to look into further.

We've also recognized the position that I think Doug Pratt enunciated this morning is that although colonization is interesting, patients are not clinically ill with it and it would probably not be a basis a licensure now. That's our understanding. And so the value of the colonization studies from that vantage may be limited.

CHAIR OVERTURF: Thank you, Dr. Siber.

We need to move on to our last speaker before we proceed with questions. So I'll ask Dr. Fries.

DR. FRIES: Okay. I will try to make this a fairly abbreviated talk. Obviously, I'm not going to replow a lot of the ground that has been covered so ably by Drs. Poolman and Siber.

I'm a rather unique representative here in that I'm representing a protein, hopefully, group common protein vaccine as opposed to a vaccine based on pneumococcal polysaccharides. And as such, the considerations and the regulatory avenues that are open to me are profoundly different.

Let's just quickly go through some of the

first slides, then I think the meat of what I have to say is in the second half of this. Because much has already been said.

In terms of the U.S. burden of pneumococcal disease in the elderly, which is the group we're focusing on, as has been said by so many, it breaks down into two categories, really. Invasive disease which is a mixture of bacteremia without a focus, pneumonia with bacteremia and relatively uncommonly in the elderly, meningitis, but it's certainly there with the cited levels of incidence of disease and mortality. It does have a disproportionate impact among blacks and, obviously, occurs with an increased rate in the risk groups everyone has identified.

The other target of opportunity and of interest is, obviously, community acquire pneumonia or CAP. Somewhere between 350 and 620,000 hospitalizations per year. We do not know what proportion of that is due to pneumococci. You'll see estimates everywhere from 20 to 60 percent, I would say. One would be very brave to actually assume it's

above 30 percent, and so I won't.

You've seen this before. The indirect impact of the conjugate vaccine administration to children and the elderly with the declining rates of IPD in the elderly since the introduction of the conjugate vaccine. In children we know there is an increasing rate of non-vaccine serotypes, as is shown in the right hand panel. And in Lexau's most recently published data, which has been referred to earlier, what we can see is that the upper portion of those bars in 2001 and 2002/03 which represents the non-vaccine serotypes and the serotypes which are represented solely by the polysaccharide vaccine are sneaking up in absolute rate in the elderly population even as the absolute numbers are declining in response to the conjugate. In fact, over this period of time that increased absolute rate is actually some 11.6 percent. This is a very short term experiment, an observation, but obviously the behavior of those upper two pieces of the pie there deserves continued observations and is one of the things that interests us in approaching base vaccine.

Evidence regarding pneumococcal vaccines in the elderly has been outlined fairly carefully. I will not spend a great deal of time on it. In terms of invasive disease, there's no compelling evidence from randomized trials in the elderly. South African gold miners, yes. But not the elderly. Meta-analyses are heterogenous and they're still underpowered, but obviously the vast burden of observational cohort in case control studies monotonously show somewhere between 45 and 65 percent efficacy. And I don't think anyone's going to question that.

For community acquire pneumonia, however, there's no evidence in controlled studies, again. Observational studies are heterogeneous often, although not always, quite underpowered. Meta-analyses aren't particularly helpful either. So there's a suggestion of an impact but the data are variable and they don't point as strongly in any direction.

In terms of cost effectiveness the 23-valent vaccine is generally believed to be acceptably cost effective in the elderly. There have been a

variety of analyses featuring multiple different assumptions, but all of them suggest that it's cost effective. Essentially based on IPD alone.

Now, as I said earlier, ID Biomedical's approach is fundamentally different. Our candidates are chimeric protein, which represents immunodominant and surface-exposed domains and, (2) conserve pneumococcal proteins in a fusion protein. It's current configuration is an aluminum adjuvanted injectable. We do believe it's capable of development in both aqueous formulation, which we're looking at particularly for the elderly where it's actually proved quite promising. And I will potential for mucosal formulations. We haven't gone there but it's something that the protein nature of the vaccine opens up as a possibility.

Now, why go to a protein after all, and particularly a group common protein? And in this table I think we look at some of the features.

In terms of serotype coverage whether you have a polysaccharide vaccine or a conjugate, you always have to some extent the limited array of

serotypes that's possible to cover. And you can be victimized a little bit by geographic diversity in terms of how good your coverage is in any particular area.

For a group common protein based vaccine you can potentially cover all pneumococci. And our studies to date suggest that our antigens are expressed on 99 plus percent of over 400 strains that we've tested so far, and we're still going.

Serotype substitution has been discussed extensively in terms of what's already happened in children and the suggestions that are occurring in adults. We don't really know yet its importance in adults, but with a group common protein based vaccine serotype substitution is not an issue.

On the other hand to be fair the possibility of escaped mutants in a protein is an issue. That's not the case with a polysaccharide vaccine. So that's a little black mark that has to be followed carefully with our product. One of the things that we hope helps avoid that is we include sequences from two separate proteins in the product.

In terms of the complexity of manufacture, ours is relatively low. It's a single high yield recombinant product. And certainly the complexity of manufacturing releases has to be higher for conjugate -- for polysaccharides of any sort, but especially for conjugates.

T cell help with our product is intrinsic, it's a protein. For polysaccharides you require conjugation.

And as a correlate of that our early data, at least, suggests that this product boosts very effectively at short intervals and at longer intervals in the elderly and is quite safe doing it, whereas boosting, as you've heard, with the 23-valent polysaccharide is mediocre, to put it generously, with some safety concerns. And it's certainly better for conjugates.

Last, but not least, we feel we have a strong potential for eliciting a mucosal immune response.

Without going into great length of data, we have carried out a number of clinical trials. And

as part of those clinical trials we've been able to show passive protection in animal animals with doses of antibody from immunized subjects that would provide about 5 microgram per mil of antibody to the conjugate antigens in the animals. This happens to be data from a lethal pneumonia model where we've been able to show about a 10,000 fold reduction of bacterial counts in the lungs of immunized animals. You can see similar results with a sepsis model. And this can be done both as active immunization and by passive transfer of immunized human serum.

And without going into details, the basic mechanism of protection appear very much the same as those induced by the current vaccines. You have complement, dependent and phagocyte dependent, opsonophagocytosis. You can absorb out the specific antibody and it goes away. So it's antibody complement in phagocytes, much as the polysaccharide vaccines.

Now having gone through that there are quite a string of challenges and different challenges in the development of a pneumococcal group common

protein vaccine. There's, obviously, a vastly smaller amount of date, although we're actively gathering it regarding the prevalence of protein antibodies in the normal healthy and ill human populations and their relationship to underlying disease rates.

Current assays of functional antibodies which you've heard discussed at great length here, are opsonized for polysaccharide antibodies. And when we try to use these same assays with our product, we get a single but it's profoundly confounded by the presence of polysaccharide antibodies. And sorting it out and opsonizing the assays to detect the induction of opsonic activity specific for these proteins you have to ring changes on the assay, which is already the product of decades worth of optimization and validation.

There's certainly no consensus regarding the protective level of any pneumococcal protein antibody. And to the extent that there's argument with polysaccharides, there's no information with regard to these proteins and antibodies to them.

And lastly, and to us the major concern is

that we think that clinical trials for a licensure of this product in the elderly or, for that matter, in the young will undoubtedly require clinical efficacy. But for some of the reasons you've heard in Dr. Siber's presentation, we're going to have to do some new thinking about endpoints that would lead to feasible clinical trial designs. Clinical trials targeting invasive pneumococcal disease will be huge. I was glad to see that Dr. Siber's numbers validated my estimate that we'd be somewhere between 300 and 600,000 subject years of observation to show efficacy against invasive pneumococcal disease in the elderly.

If you do trials looking at all cause CAP, they're actually better than the IPD trials in terms of size, but they're still dauntingly large because of limited of efficacy attainable. I would question whether it's really rational to posit 90 percent efficacy against an illness in a heterogeneous population of people with comorbid conditions, and elderly. And that being the case, you're looking at reductions of a fraction, 15/20 percent efficacy at most in CAP trials. So they're large not because the

endpoint is rare, but because the efficacy you can have is so low.

And in all of these trial size and the duration are somewhat fungible, but the trial has to make sense from a corporate perspective. And, frankly, neither of those endpoints do.

So, a couple of problems -- and I see this is the wrong presentation. Oh well.

How is licensure of a novel pneumococcal vaccine for the elderly to be approached in the States when there is one or, by the time we get to doing it, more pneumococcal approved and, indeed, recommended by ACIP but there's no data from controlled trials in U.S. elderly populations that really addresses any endpoint and there's no consistent dataset even from observational studies on the more common and the more feasible endpoints of clinical interest, like pneumococcal CAP?

And I'm sorry. That seems to be the wrong presentation. But let me just finish with a brief statement.

We think that we will have to consider

actually looking at validating some alternative clinical endpoints, things that can allow us to provide a presumptive diagnoses pneumococcal community acquired pneumonia. And that if you do that, some potential diagnostic modalities other than blood culture allow you to increase your rates of that endpoint by five, six, seven fold. And then you are looking at feasible trial sizes, still large but feasible.

There is a second bomb hidden there, which Dr. Siber mentioned, that is everyone has to agree on a definition of pneumonia. But we have to look at the available diagnostic modalities and say what can we do to really validate these so that they're acceptable to support licensure of a product.

A second set of issues comes from the fact that, no, I don't think we can do these are placebo control trials, at least not in the United States. There are probably plenty of places that we can do them. But if so, we have to think about in advance what the body of bridging immunogenicity data to bring them back into the United States really is. Whether it

requires a functional assay, whether it requires a rebuilding 20 years worth of work in opsonophagocytic assays but this time targeting and optomizing those assays for a protein antigen.

And last but not least, whether we will have to eventually do trials in the United States one way or another in which we go head-to-head with a 23-valent polysaccharide. We, frankly, would find that hard to justify giving that there's virtually zero consistent evidence of efficacy of that product for a CAP endpoint.

So I think that these are some issues that we would like to put before the Committee in discussing not the problems of how to license a vaccine for the elderly based on immunogenicity, but rather how can we make it feasible to do efficacy studies in this population.

Thanks.

CHAIR OVERTURF: Questions, comments? Dr. McInnes?

DR. McINNES: Mr. Chairman, is it permissible to address a question to a previous

speaker right now?

CHAIR OVERTURF: Yes, there's a moment. Yes.

DR. McINNES: I'm wrestling a little bit with what I think is a very beautiful paper from the PI Fry, the first author and this model developed looking at what sorts of reduction in disease you might get by looking at the 23-valent versus the conjugate pediatric formula versus 9-valent and 11-valent, etcetera. And, admittedly, the paper is published in 2002 and was looking at serotype incidents at that time in order to give proportional rates that you could expect for those particular serotypes that you might impact on.

I think if I look at those data, which really the disease reduction attributable to the 23-valent polysaccharide model looks very much like the 7-valent pediatric with slight increments as you start to add serotypes through the conjugate. The problem has come in with some of this increased disease being seen with different serotypes than were seen back in the early 2000s, and in particular the concern about

19A and perhaps some other serotypes.

Coupled together with the discomfort that some are expressing that for the non-inferiority purposes who they seem to be uncomfortable about not having an equivalent number of serotypes for this new candidate versus what the previous licensure was based on. So I'd like to find out from the manufacturers how flexible they feel they could be to respond to the need for a changing formulate as the epidemiology might suggest certain serotypes are becoming more prominent? And I'm not suggesting that we have an annual X science like we do influenza, but what would be the feasibility of having some flexibility that could respond to needs for changes in formulation of a conjugate?

CHAIR OVERTURF: Any takers?

DR. POOLMAN: You want your name?

CHAIR OVERTURF: We know your name, Dr. Poolman.

DR. POOLMAN: So far we've been thinking more about adding serotypes and we have the experience with the 10-valent pediatric conjugate vaccine. And

with respect to the adult situation, we're thinking more currently in the concept of adding serotypes. But we don't know how many. But we currently are not thinking in the context of 23-valent conjugate.

And what if we would have something somewhere in the middle, and there is a need at that stage, I would say, let's wait and see. If you are in the range of 13, 14, 15 the difference with 23-valent becomes not that big anymore. And the major differences in immune responses are so significant I'd have a hard time thinking that it's actually not going to perform better. But if one particular serotype then dramatically stands up and becomes a major relevant serotype and it's not an existing vaccine, yes, we will add it.

DR. SIBER: Pamela, you're posing a very important question because it will be an ongoing concern, not only over time but to address different serotypes needs in different countries. And I think it's a question not just for manufacturers but for manufacturers and regulators together.

Right now the average development time for

a vaccine is 12 years. And many of us are struggling to shorten that time, but we certainly aren't going to shorten it to one or two years in any reasonable time frame that we have before us. And some of these things are now on a course of now four years in the direction of pneumococcal conjugate vaccine in children.

We have one single vaccine where we make changes on a regular basis, and we've built it into the system. And so I think a question your posing is, is there a way for us together with regulators to find a path picking from a menu and not having a 12 year development plan with all the attendant safety and non-inferiority da, da, da, da to be able to reformulate it, especially unless one has more experience with conjugates as we have now.

CHAIR OVERTURF: Dr. Word?

MEMBER WORD: I guess just on that note when you talked about trying to reformulate it, the question then I'd come back to is if the Committee is struggling with looking at non-inferiority, what happens if you want to add a serotype that isn't in one that's currently there, then how is the Committee

going to determine that? I mean, if efficacy trials can't be done now because it's too many, it would be challenging and almost impossible then if you say yes, we could probably substitute, but then if it wasn't in the 23-valent before, then how are you going to make that decision? I don't know if it's something to think about.

CHAIR OVERTURF: No, I think it actually it bridges on some of the questions that we're talking about today, although I don't really find -- I guess I'm opening up the discussion a little bit. I don't really find a problem with comparing only a portion of serotypes for immunogenicity and equivalency that overlap that a portion of a licensed product. And I think that's actually the problem we're dealing with today. But I think the question you bring up, which is how do you deal with a new serotype that's not in a product that's currently licensed, and that will actually bring up some new challenges.

But it's possible that with time and if we can gain more data regarding both surrogate antibody levels or avidity or optimization antibody we may be

able to define those things. And if we can define them by incorporating them in current trials, it may be that future decisions regarding addition of new serotypes may be a little bit easier.

Dr. Self?

MEMBER SELF: Yes, it does strike me that some of the serotypes specific results that have been presented today would be a reasonable path forward. Perhaps there are some different ways that that data could be looked at and some sense of what the similarities are across serotypes could be used to borrow strength across the serotypes that we actually have data for.

CHAIR OVERTURF: Dr. LaRussa?

MEMBER LaRUSSA: Just a question for the manufacturers. Do you have any thoughts about whether there are technical limits to the number of serotypes you could put in the conjugate vaccine? I mean, is it even technically feasible to think about a 23-valent conjugate vaccine?

DR. POOLMAN: It's hard to give the limitation, but one of the nice things about conjugate

is you much lower doses of polysaccharide and usually you use ratios like one and one and one and two the protein. So the total content of material is actually much lower as compared to polysaccharide vaccine. So from a physical perspective putting it together I think that could go up to 23. And with immune responses we have to wait and see. There has been evidence that with an 11-valent conjugate vaccine from colleague that that was immune interfaces, probably carrying use suppression. We'll have to wait to see. But physically I think it's doable. Immunologically we'll have to investigate.

And may I pose a question with respect to the issue of incomplete coverage as compared to 23-valent and not making a 23-valent conjugate. One obvious solution is to give the 23-valent after the conjugate. Then you secure that you have the same and you do more. And in that sense, I have a question to Matthew Moore. With respect to serotype 19A coming up is there a difference in the elderly that were recently immunized with 23-valent, do you have the information of that or is it different in nonimmunized

or immunized the elderly?

DR. MOORE: Unfortunately, again, I have to say the short answer is I don't know. From the routine surveillance data it's difficult to rely on the vaccination information that we have. Because, as you know, adults can be vaccinated in lots of different places and that information is not always readily available from the medical chart.

We are in the process of finishing up a study where we may be able to look at that sort of information, but we're not there yet.

DR. POOLMAN: I think it's crucial information, it's the currently most relevant serotype. And if you can prove that the existing vaccine is still working there, then the sequential immunization conjugate first polysaccharide later will resolve questions on losing of coverage.

CHAIR OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: Yes. Isn't it highly unlikely that we'll be able to coordinate those events so that the vaccines are made by two different companies or three different companies, or whatever,

that we'd actually be able to give the 23 and then -- I'm sorry. Give the conjugate and then later give the 23? How would you think that would get coordinated in the public?

DR. POOLMAN: I think similar situations exist in pediatric scheduling with different manufacturers where you have boostings with different compositions of vaccine. I don't think that should pose any issue.

MEMBER MARKOVITZ: Traditionally, with adults it hasn't been that easy, though. Unfortunately. And I agree it would be nice, but it's typically not that easy with adults.

CHAIR OVERTURF: Dr. Karron?

MEMBER KARRON: I was just wondering about data that we have so far perhaps from children on duration of protection from conjugate. Because I'm wondering from what you presented, George, you talked about the fact that once you give polysaccharide you're sort of stuck in this hyporesponsiveness mode. So it occurs to me that if we're talking about a sequential immunization potentially of conjugate

followed by polysaccharide, well then we should hope that the conjugate provides very long term protection if, say, we're talking about immunizing a 65 year old who might live for another 20 or 25 years. Because once you give the polysaccharide, then perhaps you can't give another dose of conjugate. And I don't know if someone wants to comment.

DR. SIBER: Ruth, you raise an interesting question, which is once you've primed with conjugate, if you will, and give polysaccharide will you then have again, a hyporesponsive problem? It's actually not something that we've looked at and probably it deserves to be looked at.

The matter of duration of protection with conjugate themselves, we actually have in children very good data now for prolonged protection from conjugate. I think the ABC data show that, the Finnish with titus media study actually shows a very substantial protection for titus media over a long period of time, up to five years. But in adults, of course, we don't have any data at this time and that will have to be monitored closely in use. And I think

what you're suggesting is we probably should look at whether polysaccharide after a conjugate has some form of hyporesponsiveness inducing effect as well.

CHAIR OVERTURF: George, I'd for you to address one additional question. It seems to me that you bring up actually almost an ethical question about whether you could use non-inferiority comparisons to polysaccharides in adults, whether you think it's ethically responsible to continue to give polysaccharides, whether there is sufficient data to suggest that perhaps we shouldn't be giving polysaccharide to adults and whether that can continue to be one arm in a study in which you may be subjecting a group of adults to hyporesponsiveness?

DR. SIBER: Gee, I don't think it's quite that bad. Only because, you know, look at the data for polysaccharide vaccine itself. You have solid efficacy for five years, continued efficacy for a period of time, albeit waning. And there's no question about the efficacy of polysaccharide vaccine, in my opinion. So to say that it suddenly becomes unethical to use it based on our immunologic

observations I think would be taking this too far.

CHAIR OVERTURF: Dr. Word?

MEMBER WORD: Just to follow-up something that Ruth said. You know, she was talking about adults living longer and receiving the vaccine sequentially. I was thinking about in the pediatric population, they're high risk children that they get a dose of conjugate and then they get a dose of the polysaccharide. And they're going to live a long time. So then have you looked at that? Has anybody looked at that? Are you thinking about looking at it?

DR. POOLMAN: There are some nice studies published with meningococcal C, which is a good example of a polysaccharide, and it uses hyporesponsiveness. And a British study group from Oxford did rather complex studies of polysaccharide, polysaccharide or conjugate polysaccharide. And the essence message is you can -- you come with conjugate, you come with polysaccharide; you couldn't reduce some level of hyporesponsiveness. If you come back with conjugate, you resolve it again. That was, I think, my take on message from these complex studies.

And I agree with George, the hyporesponsiveness is there but it's not something that should withheld of a polysaccharide vaccine. And there are ways to resolve it, as has been shown with meningococcal C conjugate.

You should not give the polysaccharide twice. I think that's what we reaching to that conclusion.

CHAIR OVERTURF: I think we'll proceed to the presentation of the FDA questions.

DR. GRUBER: My name is Marion Gruber. I'm with the Office of Vaccines, Research and Review.

And, Mr. Chair, with your permission before I'm going ahead and restate the discussion points that I presented to the Committee this morning, I would like to make a few remarks to the Committee or the Office of Vaccines, Research and Review would like to make a few remarks to the Committee. Remarks that are unprepared and were not rehearsed, but we felt that it is important to make these points before we get into the discussion points, the presentation of the discussion points.

The subject of defining for licensure and defining licensure criteria for new generation pneumococcal vaccines to prevent pneumococcal disease has been a difficult subject to address, not only for infant indications or pneumococcal vaccines for infant indications, but also for the adult indication. And it has been a subject that kept the FDA, the Agency very busy. We had a lot of discussions, meetings with the vaccine manufactures. And we have been discussing these issues that you have been hearing this morning for a number of years.

And as you heard or have heard, the issues are issues are very complex. They're very difficult, not only looking at the difficulties to perform clinical endpoint efficacy studies, diagnostic criteria, clinical endpoints, sample sizes but also, if you will, some of the uncertainties that surround inferring efficacy based on a immune criteria. So the discussions you've heard today really summed up discussions that we had for some of the manufacturers over the last two years, at least.

And we felt that it was important at this

time to approach the Committee for their input and advice. Because we felt that we needed an additional opinion before the Agency goes and formulates a regulatory framework. And it appears that the extent of the data that you have been hearing today and that have been presented to you is the extent of the data that we need to use to base some regulatory framework for licensure pathways for pneumococcal vaccines for the adult indication on.

So I would like to then restate what I said this morning, what the Agency really would like for you to discuss today is the most appropriate pathways that you think -- or what the most appropriate pathways for licensure for pneumococcal vaccines are for the adult indication taking into consideration the various vaccine types that have been discussed this morning.

Again, there will be no request for formal vote. But what the FDA will do is utilize the advice that we receive today from you to formulate a regulatory framework for pathways to licensure for pneumococcal vaccines for adults. And I would like to

proceed now with the discussion points.

Number one: Please discuss whether non-inferiority immune response studies comparing a new pneumococcal conjugate vaccine to the license 23-valent pneumococcal vaccine PNEUMOVAX 23 for common serotypes can be used in lieu of clinical endpoint efficacy studies to support the approval of an indication for the prevention of pneumococcal disease in adults.

1A: If non-inferiority immune response studies are considered sufficient to infer efficacy, please identify the appropriate immunological parameters for use in such studies.

1B: If clinical endpoint efficacy studies are considered necessary to support licensure of the new pneumococcal conjugate vaccine for prevention of pneumococcal disease in adults, please discuss the appropriate target populations and endpoints for the study.

1C: Please discuss what additional data should be requested to support approval of an adult indication for a new pneumococcal conjugate vaccine

that would contain a subset of the serotypes contained in PNEUMOVAX 23.

Discussion point number 2: Please discuss what studies would be necessary to support licensure of pneumococcal vaccines directed against noncapsular pneumococcal antigens for the prevention of pneumococcal disease in adults.

And finally 3: Please discuss other possible approaches to support approval of pneumococcal vaccines for the prevention of pneumococcal disease in adults.

Thank you very much.

CHAIR OVERTURF: So the Committee members have 15 minutes to come up with those answers.

We'll convene at 25 minutes after 3:00. Thanks.

(Whereupon, at 3:15 p.m. the Committee recessed until 3:30 p.m.)

CHAIR OVERTURF: I think all the Committee members have -- there will not be a formal vote on these questions, but what CBER and the FDA needs is our discussion on tape so they can prepare a

transcript that will actually help them develop policy.

So I think the best way to do this is the way we did it yesterday, which was to go around and get everybody's comments and to try to address the three questions and the subquestions for number one.

so, Dr. Wharton, could I start with you?

DR. WHARTON: Sure. I think the way I see this is very much colored by the really striking information in the background papers that apparently the indirect benefits of using pneumococcal conjugate vaccine in children among the elderly exceed the directed benefits of using the pneumococcal polysaccharide vaccine in that same target population. And if we want to do something about pneumococcal disease in adults, we clearly need a more effective tool than we currently have. And certainly the conjugate vaccines appear to be very promising.

That said, we still need an appropriate body of data to support their licensure even under accelerated approval. And I'm uncomfortable with relying only on immunogenicity to do that, even under

an accelerated approval scenario where subsequent studies would follow. It's too unclear to me what OPA activity actually means in an old person who may have impaired phagocyte function and all kinds of other things going on that are key components of the immune response.

So although the data that have been presented on the immunological correlate are interesting and clearly deserve further study, I'm not sure I'm comfortable going with that for licensure.

That said, the clinical trial scenarios that have been presented as daunting. And it's difficult to imagine some of them being feasible to perform. One discussion that we haven't had here is to what degree the polysaccharide vaccine is the standard of care in European countries where we commonly perform clinical trials, and perhaps a study among the elderly could be performed in Europe that would not require use of a polysaccharide as a comparator. But they're difficult to think about how those trials would actually work prelicensure.

So I want to go back to the issue that Dr.

Farley raised earlier about carriage studies. If the prevalence of carriage in elderly persons who don't have contact with children is in the range of one to five percent, which is approximately Dr. Siber said, presumably it is higher among elderly persons who do have contact with children. And so the question that I think deserves some reflection is given that that is a highly specific endpoint, albeit not one that has clinical benefit to the person who is not carrying the organism, it presumably is an intermediate step in development of disease being colonized. And so is this something that warrants the exploration, at least as a first step, in accelerated approval that could then be followed up with the sort of very elegant study that Dr. Jackson and others have done using managed care database post-licensure.

So that's my thinking on the issue of licensure of a pneumococcal conjugate vaccine for use in the elderly.

As far as what additional data should be needed to support approval -- oh, and another advantage I think of looking at carriages we assume it

wouldn't be impacted by prior vaccination with the polysaccharide vaccine. So that's another bit of noise that would fall out if we took that approach.

Clearly I think it is necessary to have information on subsequent vaccination after use of it with the polysaccharide vaccine after a conjugate vaccine to make sure that there maintains the ability to add those additional serotypes if the conjugate vaccine doesn't contain all of them, which we don't expect it to.

In terms of what studies would be needed to support licensure of the pneumococcal vaccines directed against noncapsular pneumococcal antigens, I don't know enough about how these vaccines would work to know if something like carriage even makes any sense. I don't know that. It may be essential for that type of vaccine to do an efficacy study pre-licensure. But I don't know. I don't know if there's alternatives that would make sense to use.

And as far as other approaches, again, I think it's worth thinking about studies in populations where use of the pneumococcal polysaccharide vaccine

isn't the standard of care among the elderly where the rates are higher to see if clinical trials might be feasible in those settings.

CHAIR OVERTURF: Dr. Self?

MEMBER SELF: So for the first, I guess I'd split this up into two pieces. One has to do with the use of an immune response as a correlate. The other has to do with its use as non-inferiority.

There are fairly specific criteria for the use of immune response and responses in this way, and I actually don't see that direct empirical evidence connecting it in this case in OPA or ELISA to protection in the target populations. And so it's hard for me to see that that would be -- there's a clear basis for using that here.

There are other types of arguments that seem to me to build a strong case for it being a possible correlate of protection, but that's a somewhat lower bar. And I find the argument of well what else could it be if it's not OPA not particular compelling. I mean, I think this is a case where we, to quote somebody I'd rather not quote, "we don't know

what we don't know." And that's difficult for me to get over.

So I would be very much wanting to avoid the use of that measure as an indicator of licensure.

So that brings the issue to the other clause, the other types of criteria where this could be used, and that has to do with trial feasibility. Now cases were made that standard trial designs, efficacy trial designs would not be feasible to conduct, and there are all the problems laid out about endpoints and the rates of those endpoints int he various target populations. I honestly can't tell from the discussion that we've had today and reading the papers what the answer is, whether there is truly not a feasible way to do a clinical endpoint study. And so it's hard to say right now whether that kind of trumps my reservations about the use of immune correlates.

My best recommendation, I suppose, about this would be to have some sort of exercise performed that would involve a number of people from the Agency and maybe beyond to talk about a little more creative

designs that might be used, perhaps designs that would capture both direct as well as indirect effects. And try and come up with some wisdom at the end of a more detailed exercise that everybody joins in, perhaps, together.

So at the end of that, it's my turnout that this is not something that is feasible. And then you are sort of forced to return to these immune response measurements. Even at the end of that trail I have serious problems just with the issues of the valiancy. So I can't think of any way right now to calibrate the potential increase in efficacy that might come from the common serotypes with the lack of coverage for the serotypes that are not included in the new vaccine. And somehow that has to be addressed.

You know, one thing that's completely clear in my mind is that the non-equivalence based on just the set of common serotypes is not good enough as the basis for licensure. So there has to be something more to the argument than what we've seen today, at least in my opinion.

I think I will also pass on the question about noncapsular pneumococcal antigens. And I think my comments I hope at least glanced to question 3 about other approaches to support approval.

CHAIR OVERTURF: Dr. Jackson?

DR. JACKSON: Well, I agree that there are a number of dilemmas. One is that giving a lower valiancy conjugate vaccine inherently has a disadvantage in comparison to giving the 23-valent polysaccharide vaccine. So the non-inferiority immune response criteria runs into some problems in that regard.

I would say that if we're looking at age groups and population groups for whom no pneumococcal vaccine is currently recommended, then if you were to establish non-inferiority to a vaccine that we believe is effective in some groups, that group would then be benefitting. So, for example, people 50 to 64 who don't have chronic conditions that are an indication for vaccination currently, perhaps a non-inferiority approach would be sufficient to say that those persons could receive a conjugate vaccine. In other groups,

however, you're trading off the current standard, which is to give the 23-valent polysaccharide versus a new approach, which would be to give the conjugate, and it's the difference between the sera group coverage that potentially puts those people at higher risk of pneumococcal disease in general. And so then risk would have to be balanced off against some other advantage. And the advantage could be that there's a higher protection against the sera groups in common to both vaccines that the increased effective of the conjugate vaccine to sera groups in the conjugate vaccine itself would outweigh a decrease in total number of sera groups, potentially, or that there's an expanded spectrum of coverage of disease protection against community acquired pneumonia for example or that there's an expanded duration of protection. However, I don't think that any of those advantages can be proven with a non-inferiority immunologic approach, which is the crux on the dilemma.

On the hand, I think that most of us or all of us want a better pneumococcal vaccine for adults. On the other hand, what should be the

standard proof that would be required for licensure of a new product that in most cases would probably be used instead of the current standard of care?

So that does run into the very real issues of feasibility of clinical trials that we've been discussing today. There are perhaps some assumptions that could be questioned that might allow for more reasonable sample sizes. And one would be whether hyporesponsiveness induced to the polysaccharide persists forever or for a very long period of time. Because if it doesn't, then you could enroll people that receive the vaccine at age 65 and who are now 75 or whatever, beyond the period in which you'd expect any effect, positive or negative, of previous vaccination to now have been resolved. And in that case you could ethically do a placebo controlled trial in which you randomized persons to conjugate or protein or whatever type of vaccine or placebo. And you also have the advantage of higher disease rates the older population group you study, both for invasive disease and for community require pneumonia or specifically for pneumococcal pneumonia. The

disease rates are still not really high, though. So, I mean, there would still be very real issues of sample size and feasibility.

Let's see, moving to the appropriate immunologic parameter that could be used in non-inferiority approached. I don't know. I would suspect OPA at some level that's considered reasonable indications there is true opsonic activity, I don't think we would need to prove higher levels. But just a threshold established which would then be met for the sera groups included in the vaccine would be sufficient.

If clinical endpoint studies are considered necessary, again I said perhaps the older end of the spectrum of previously vaccinated persons that was considered to be a feasible approach could be used for conjugate approaching vaccine studies.

Additional data, I'm sure who would pursue this. But it seems like this issue of hyporesponsiveness to the polysaccharide vaccine is important in considering the relative benefit of the use of alternate vaccine strategy. And so maybe we

need to know more about that. Although certainly it seems well demonstrated that you get a decreased antibody response to a subsequent dose of polysaccharide given within one or five or possibly longer years, I'm not aware of any clinical data that would suggest of putting those persons at risk of actual increase in disease. I mean, if we don't know the threshold correlate of protection, we don't know whether lower antibody has any meaning or not, although intuitively we would be concerned about that.

For noncapsular antigens, I think as has been discussed some sort of efficacy trial would be required for that. And other approaches, post-licensure work will be important and the major questions then is what degree of pre-licensure data and evidence are required to get to the post-licensure stage.

MEMBER KARRON: I guess I'd first like to echo what Dr. Wharton said in terms of our sense that we need a better vaccine for the elderly. I was struck in listening to all the discussions today that on the one hand we don't want to set the bar so high

that we actually discourage companies from pursuing this goal. And I'm actually concerned about that. I'm concerned that if we mandate efficacy studies, for example, that certain individuals may decide to pursue this and that we will be left with exactly the vaccine that we have for the elderly right now, and that is a concern for me.

On the other hand, I think the other thing that -- the difficulty that all of us are having is this issue of an existing 23-valent vaccine and thinking about other conjugate vaccines of some lower valiancy number. I think we heard from Dr. Moore today that this issue of replacement phenomena is sort of a moving target. We don't exactly know where we are or where we'll be with that. I do think that still, though, in terms of looking at the numbers thus far the numbers are relatively small. But that this is making a fairly small contribution to the overall disease burden.

I guess I would like to dissent a bit and open the door to the possibility of some non-inferiority studies looking just with invasive

bacterial disease as endpoint. I certainly don't think that you could do that for community acquired pneumonia. But I would want to think about that for a conjugate vaccine.

I think that we do need to think about at this point using a conjugate vaccine in conjunction with the 23-valent vaccine. And so I would like to see additional studies, as we've discussed earlier, of a conjugate vaccine followed by a 23-valent vaccine and looking at duration of protection and then looking at what happens if you in fact come back with a conjugate vaccine again. Do you just giving the 23-valent vaccine induce hyporesponsiveness?

I guess sort of an answer to the question 1A about the appropriate immunological parameter, I think OPA is probably the best that we have to look at that.

I guess the other comment that I would like to make is that as we consider studies and we think about target populations, we shouldn't just think about -- I feel very strongly that we should not look at surrogate populations for the elderly, we

should look at the elderly. So we should not be doing studies in 50 to 65 year olds. We should be doing studies in those over 65. And I think also among those over 65, we need to look at a range of ages. So we need to look at the elderly. And I think we need to look at the very elderly.

And the only other comment I think I'd like to make, which I think is clear from what other people have said, is that in terms of thinking about non-capsular pneumococcal antigens, then clearly I think we do need efficacy trials.

CHAIR OVERTURF: Dr. Piantadosi?

DR. PIANTADOSI: Thank you. My comments are not structured in the same way as the questions, but I'll go through them and I think I'll cover most of the important points.

In my judgment the essential problem at the heart of the FDA questions regarding development of new vaccine for pneumococcal pneumonia is the classic debate about validity of surrogate outcomes. In this case OPA is the proposed surrogate. And the question is whether or not it can substitute for

definitive clinical outcomes in vaccine development, such as clinical pneumonia attributed to pneumococcus or invasive disease.

The questions surrounding OPA are made somewhat difficult by it being a laboratory measure, however well standardized, rather than a surrogate clinical outcome. Guidance on this classic question is abundant in the methodologic literature. The validity of OPA as a surrogate for prevention does not depend on the information presented today.

For example, it is not definitively valid because it seems to measure a vital component of the immunological response to established infection or because it is statistically correlated with other immunological measures. Nor would it be valid even if it were correlated with a definitive clinical outcome.

The validity of OPA as a surrogate depends on its tracking direction and relative magnitude, the same way as the definitive prevention outcome after vaccination. This is basically the Prentice criterion applies in this context. No data with this strength of evidence or quality have been presented here today.

The difficulties with OPA are illustrated in a couple of its characteristics. It does not appear to correlate quantatively with clinical outcomes in adults. Even if endorsed for polysaccharide vaccines it would be irrelevant for protein constructs. Thus, OPA has not minimal standards for a surrogate outcome.

With regard to non-inferiority my opinion is that the difficulties of quantitative interpretation make OPA especially ill-suited to design an interpretation of those kinds of trials.

OPA is an appropriate outcome on which to base developmental decisions and can be used to increase the reliability of developmental choices and reduce the risk of failed comparative trial.

I am also concerned and sympathetic to the potential problems of doing large randomized trials in prevention, and this context seems particularly difficult because of issues such as bacterial subtypes, difficult diagnostic criteria and incomplete efficacy. But such problems are not cured by doing smaller trials with a potentially invalid outcome.

Another potential problem in the future

from such an approach is having economic and ethical imperatives, perhaps wrongly, established for suboptimal treatments by our health care system. This can make clean definitive studies more difficult for new preventives and therapeutics.

I would close by mentioning a couple of ideas that have not come out in today's discussion, but that might make adequate and well controlled studies more achievable.

In the presence of a relatively safe intervention, as vaccines seems likely to be, it makes sense to relax the type 1 error in our study designs. This would be breaking ground for the FDA, but it's appropriate to set such criteria to reflect the consequences of making the respective error. For example, for a safe intervention a type 1 error rate of, say, 10 percent or higher might be appropriate and would help reduce the size of the studies needed.

The FDA and sponsors should also consider alternatives to the standard designs that were displayed today, mostly for their seeming lack of feasibility. I'll mention three possibilities, not

because I know them to be appropriate in this context, but to try to broaden the thinking and discussion about study design and methodology.

First are cluster randomized designs where although the total sample size of individuals would be large or larger than those mentioned, the logistics of the trial might be more manageable than individual randomizations. Units of randomization might be taken to be residence homes, group practices or even entire cities for example. These are the kinds of trials that have historically been applied in developing countries to investigate prevention interventions.

Second, some consideration might be given to factorial designs constructed in a way to use their potential efficiencies. Pairing the pneumococcal vaccine question with another prevention question, for example, might make for more active participation by adults and practitioners alike. I think it's important to note that factorial designs are not always more efficient, but when designed properly you can get a two to one efficiency.

Finally, single cohort designs with

definitive outcomes may have a role here as well. They can in principle provide the kind of evidence needed and would be made more reliable by the CDC surveillance data that we were shown earlier.

Thank you.

CHAIR OVERTURF: Dr. Steinhoff?

DR. STEINHOFF: I agree with many of the comments made. I'll just reiterate some of them and add a few points.

I think with regard to the first question about non-inferiority as a way of moving forward, it seems to me that aside from the point of fewer serotypes, which is a major point, there's no reason not to use that criteria to license a conjugate vaccine. We've heard there's historical precedent for doing that. And if it can make as much antibody of whatever type as an existing vaccine, even though the overall serotypes coverage is less, it would seem to me that's something one could still do. It leads for implications for what you do after you license such a vaccine, because if it is in fact more effective on fewer serotypes, the overall impact might be greater.

The other point, though, with regards to non-inferiority, that would apply only to the connection that we've heard about, which is the vaccine is immunogenetic to some extent in adults and has an effect on IPD, culture positive disease. I don't think that the similar reasoning would apply to community acquired pneumonia where we don't have a similar confidence that the vaccine is making a difference.

So for similar indications and similar antibodies, it seems to me that is something one could consider.

You are still stuck with the problem of fewer serotypes. So one would have to postulate that there's a greater effect.

In terms of which test to use, which is part 1A, I find it very troubling that the effectiveness of antibodies is so different related to age groups. And some of the suggestions made about comparing OPA titers with adults who have received the currently licensed vaccine as a way of measuring non-inferiority makes sense. We don't have anything else

right now, unless we do an efficacy trial.

To go on to the second point about if an efficacy trial is done, it seems to me that that trial should consider something which wasn't discussed very much here, is to think about better diagnostic technologies to define what might be pneumococcal disease beyond the blood culture criteria that we've used.

We heard a little bit about looking for antigen in urine. And there are at least two ways of doing that, both of which I suspect could be refined. That would take, though, a fair amount of development work before you start the efficacy trial.

I think that the category of punitive pneumococcal disease or possible pneumococcal disease which would include a clear clinical definition with a variety of other criteria such as antigen detected in urine or blood maybe some markers of inflation, and of course some kind of an x-ray finding might give you a better indication of what disease you're preventing, even if it's somewhat insensitive or even nonspecific. My guess is that given these kinds of criteria you

could show an effect of a pneumococcal vaccine in overall CAP rates because you're focusing on what's more likely to be new.

I mentioned the crucial issue if you don't have the same number of serotypes how much can you rely other criteria.

I agree with the points that others have made regarding the non-capsular pneumococcal antigens that to license those I think you do need to have an efficacy trial. Those should be planned so that one could begin to look at the information regarding antibody levels that appear to be protective, looking at the kinds of graphs and charts we saw today. I think that could be done right at the beginning to get some indication.

Those studies, too, by the way would benefit from the category of punitive pneumococcal disease as one of their endpoints.

That's my comments. Thanks.

CHAIR OVERTURF: Dr. Word?

MEMBER WORD: I think the easiest thing, in one sense which I think probably everybody's in

agreement is, is looking at the pneumococcal vaccine directed against the pneumococcal antigens. And actually the way to go with that would be efficacy trials. I just find the whole concept very exciting and would look forward to seeing that move forward.

In terms of just going, looking at surrogate markers. You know, originally I was really excited about it, I thought this would be good. And then as I listened a little more, I started saying you're telling me this vaccine is not as protective in elderly people yet you want me to say that okay, I can compare it to something that doesn't work so well. And, okay, maybe it won't be inferior but is it the best thing because they have a hypoimmune response. Then, you know, looking at this OPA, which I learned a lot about during this time period here. I said well I'm hearing that there's differences in terms of age groups and how people respond, so it might be nice to see if you break down the ages. There's something that happens at 65, well happens at 64? What's going on between the person between 50 and 64 years of age? Maybe I want to know what the normal is there. Maybe

I want to know in a few age groups. Because people do live longer now. People are living 80, 90 years of age and it would be interesting just to see. And I think it could potentially be a correlate and something that people can look at.

Right now I'm not convinced because I'm not quite sure how to interpret it, and so I'm not as comfortable with it. Even though I'm not so thrilled by the non-inferiority with using less pneumococcal serotypes, I think if the companies had approached the conjugate vaccine with the 23-valent, it probably would have been more supportive of it because it probably would have been my own comfort level more than anything else.

And I guess I'll stop there because I don't really know what else I want to say. I've actually agreed with a lot of other things that were said, there's no need to repeat it.

CHAIR OVERTURF: Dr. LaRussa?

MEMBER LaRUSSA: Okay. I'll just go down the list.

I think the first thing is if you want to

have a really big impact on the pneumococcal burden, the idea of improving the pediatric vaccine should go near the top of the list.

As far as the first question whether non-inferiority immune response studies can be used in lieu of clinical endpoints, efficacy studies at least at this point in my opinion is no. I think it's possible to design trials, and I'll talk a little bit more about that in a second.

In terms of what the appropriate immunologic parameters to look at, I'd like to hear more about the OPA assays, especially in the age groups we talked about with the appropriate controls. And I think the idea of looking at changes in colonization rates is really an intriguing way to look at a second parameters and may, in fact, answer some of the questions that we've had.

As far as the part B if clinical endpoint efficacy studies are necessary, I think we do need to look in adults over the age of 65 and come up with a reasonable definition of pneumococcal pneumonia, and I think that's possible. I think we can do chest x-ray

plus some sort of urinary antigen. It's not going to be perfect, but I think it will be a reasonable thing to look at.

As far as additional studies, I think we've got to look at these combinations of vaccines that practitioners will use, whether it's polysaccharide followed by conjugate because there's already that population out there or conjugate followed by polysaccharide followed by conjugate. And people are going to do that, so we need to figure out what exactly those combinations will do.

I think with the protein vaccines at this point we're stuck with efficacy studies.

And finally, in terms of additional approaches I think if we really scratch our heads and do not come up with a reasonable efficacy study and we do end up approving the conjugate vaccines on the bases of immunologic markers, then I think that approval has to be contingent on rereview once the large databases give us the answer about whether they've had some impact on community acquired pneumonia.

CHAIR OVERTURF: I largely agree with what's been said. I will say that clearly you can use immune studies in part on non-inferiority basis for licensure of new vaccines.

One thing it seems to me that hasn't been -- and I didn't hear any data to convince me that we know enough about the optimization assay, that can be used solely as even a single immunologic correlate. I think it probably has to be combined with things that we do understand a little better, antibodies despite we don't understand all the quality about that antibody.

There was a point made about a carriage and we heard repeatedly that carriage rates in those who have low exposures to children are low. They're certainly not what we see in children, but they're certainly much higher than disease rates. And it would seem to be an additional part of what should be added and was clearly one of the benefits and one of the additional benefits we're already seeing with conjugate vaccine use in children. So it seems to me folly not to include carriage studies as one endpoint

for evaluating conjugate vaccines even comparing them against polysaccharide vaccines.

And I would echo what a lot of people have said about the problems with dealing with a 9 or 11-valent vaccine and a 23 vaccine. And with an appropriate selection of the serotypes based on current epidemiology you could reduce the difference in potential efficacy between a polysaccharide and a conjugate vaccine to a very small number with perhaps only the addition of another, what, 3 or 4 serotypes. Because the actual number of potential coverage that you'd get with some of the additional serotypes only come up to 4 or 5 or 6 percent total. So I think some real concern needs to be thinking about adding some serotypes that come closer to matching the coverage or at least the minimizing the differences in coverage between the two vaccines.

I agree with Dr. LaRussa that I think there can be better standards set for diagnoses of community acquire pneumonia. And somebody made the comment that it is more difficult in adults than it is in children. I feel just the opposite. Actually it's

easier. Actually low bar pneumonia is actually a much easier radiographic endpoint to define in adults than it is in children, particularly if you will go the population that's at most risk for those, which was the population we are most interested in, which somebody commented on, which were the very elderly population.

Actually, that was done in the Kaiser trial on children, the ability to predict efficacy against pneumonia began to rise as the specificity occurred. The problem in children is that you're dealing with a lot of viral disease, which is not going to be effected radiographically by the introduction of a pneumococcal vaccine. But it is also possible.

I think I would be satisfied if we had a narrow enough gap, we showed striking effect on carriage because that's actually the first step in the pathogens to disease to licensing a vaccine provided there were very, very, very strict concepts of what had to be done with phase for efficacy trials. So that one could rapidly perhaps get an answer once a

vaccine was licensed.

It may be, you know if we're really talking about studies regardless of some of the manipulations that Dr. Piantadosi mentioned, I still think that we would have very, very large trials. But we are getting to the point where we are accepting trials some 60 and 70,000 in other vaccine trials now that we are doing. So that some of these I do think have a feasibility.

For the non-capsular serotypes I think you're stuck with some kind of efficacy trial.

One thing I didn't hear from those, and I assume there is no effect on carriage and so I don't think carriage would be an option in that particular kind of a trial, but it would be interesting to know.

Dr. Robinson?

DR. ROBINSON: The first thing struck me was what Dr. Moore presented and are we moving down a pathway in which a very good vaccine for infants and young people is driving the pathogen and the disease that it causes to be this phenomena of capsular switching and that are we going to see prevalence of

antibiotic resistent strains or subtypes and then also to have it be even more invasive I think that's just something that has to be watched in the future. But if this is the paradigm of where you give a capsular vaccine first followed at some interval later on with a polysaccharide vaccine, then what is going to be that interval? And then what's going to be happening during that interval especially if you say you give it to adults, which is what we were asked to address, at 50 years old followed by how many years later? Well, we saw data that it looked like three years from a Finnish study. That may be the same type of efficacy. But what if it's not until you're 65? And then we're having the infant programs that are actually driving certain subtypes to be more prevalent and more disease causing? As a conceptual thing it troubles me a little bit in how that's going to be handled.

Pragmatically though looking at different intervals from the time you receive the first immunization primarily with a capsular vaccine followed either another capsular vaccine or a polysaccharide vaccine, I think that needs to be added

in these trials.

Relative to the protein based vaccines, I think the guidance that the FDA provides for a true efficacy trials for a well characterized biological are in place there. And I think that it has to move that pathway with the development of the different diagnostic for the clinical samples.

I would like to see more emphasis on mucosal immunity and what can be done there to look at not only in terms of dates of IGG, but also with IGA and to see what really impact that has and it can be done as a subgroup of one of the clinical trials.

And finally, just looking at where is the future for these vaccines, just looking at what the issue is and how can you enhance the immunity in the elderly population regardless of what vaccine you use? And to me it looks like a vaccine and wanting some of immunostimulant, whether it be a device or an adjuvant or some other type of immuno cytokine. And so that would be a further direction down the road.

MEMBER PROVINCE: My remarks will be brief and contingent upon my ability to read my own

handwriting, because I've been jotting down notes here.

Speaking as a consumer representative, as I am on this body, what consumers want of course is safety and efficacy. And as we've heard, of course, people are living longer and they have higher expectations for their personal health. You know, I think of my aunt who is 101 years old and has lived 36 years beyond the time she would have received her pneumococcal vaccine. She's still out in the community living on her own, and she's not that unusual anymore. We see more and more people living to the age of 100 and beyond and so we can't think of 65 as quite the way we would have, perhaps, in previous decades.

Clearly with all we've heard in the last couple of days we all agree, I think, that we need something better. But as Dr. Karron mentioned, we don't want to set the bar too high. If we do that for any vaccine, we set ourselves back, we retard the development or potential development of new vaccines and we really need to look at that and be cautious

that while being very careful about the issues of safety and efficacy, that we don't set the bar so high that it's just unattainable.

I was very interested in the illusions to creative designs to show efficacy that was alluded to earlier as the standard efficacy trial designs could get to be such large sample sizes that they'd be unwieldy and unfeasible, and we're running into that more and more. So I think we need to look at some of these strategies that have been mentioned and take a close look at that.

I'd like to see some additional work in giving the conjugate vaccine after the polysaccharide vaccine, perhaps to work around the problem of the fewer serotypes that would be included in the conjugate vaccine. And, you know, perhaps in populations where the polysaccharide vaccine has not been used to use some data from those populations I think would be very helpful.

And in any event, however it ends up, I think post-licensure work -- I always feel like a broken record because I say this almost every time I

open my mouth. But I think post-licensure work is imperative, is more and more important not only looking at efficacy, but in looking at rare and very rare adverse events. And with that, I'll conclude.

DR. McINNES: I've been listening all day and reflecting back really on the last 16 to 18 years and thinking about everything we learned from hemophilus conjugates, polysaccharides and conjugates, meningococcal polysaccharides and then conjugates and then the pneumococcal polysaccharides and the conjugates. And I think we have been surprised every time about the power of this family of conjugate vaccines. And with regard to pneumonia we reflect back on the hemophilus influenza type B conjugate trial in the Gambia and the very surprising finding of the impact on all cause pneumonia reduction by 15 to 20 percent. It was unprecedented. We didn't anticipate it at all.

I would say that the efficacy data from pneumococcal conjugate as evidenced by the Kaiser trial, the otitus media trial, the South African trial, the Gambia trial has surprised us every time

how astonishingly powerful these vaccines are in protection against not only invasive disease, but as illustrated in the Gambia against pneumonia, against radiographically confirmed pneumonia, culture positive pneumonia, all cause pneumonia, hospitalization visits; these are powerful tools we have intervention.

I don't think it's a leap of faith that the primary mechanism of host defense against streptococcus pneumonia us antibody. Extrapolating from that I think the functional assessment as measured OPA assay, I think it does measure only functional antibodies. I think those are correlated with protection against invasive pneumococcal disease. And I am persuaded that non-inferiority immune response studies are sufficient to infer efficacy for pneumococcal conjugate vaccine.

With regard to the serotype coverage, I think it is very clear that this discussion is not over, and the coverage it needs to be appropriate and it needs to be responsive to changes in ecological -- and I think that's a little bit unusual outside of our influenza experience, but I think maybe this is time

to say this: We have to embrace this in this discussion if we're going to take this path. So I think we need a new system to allow that to happen.

So this multifactorial idea of thinking about immune response, quality of the antibody response, the duration of the antibody response; I think it's a compelling constellation that could be taken forward and flushed out more and thought about. But at this point in time I'm persuaded that there could be a path to licensure for these vaccines without clinical endpoint trial up front.

The induction of the functional immune response that allows subsequent vaccine if in fact it's deemed that we do need to maintain a flexible system that can give us broader coverage, not necessarily only through the conjugate I think is very interesting. And I think one should look very carefully at what data we have and what data perhaps could inform that. And when I look at the modeling paper and taken into account that we might be able to have a system with more flexibility, I suspect that we will have the same or better impact on invasive

pneumococcal disease and we'll gain protection against pneumonia with integration of pneumococcal conjugates into adult vaccine and certainly into elderly vaccine. The question is what detection systems need to be put in place to monitor that and to inform changing decisions if those are appropriate.

I think that reflects my thoughts. I don't have anything novel other than what I have heard here to contribute to the discussion around the non-capsular pneumococcal antigens. That's it.

CHAIR OVERTURF: Dr. Farley?

MEMBER FARLEY: Yes. I first of all would like to just say that I think that the idea of targeting adult populations with these conjugate vaccines for pneumococcal disease in particular is a very high priority, and I want to do everything to encourage this to go forward. And that may mean that we may have to in some ways make some compromises from the standpoint of how the process from a regulatory standpoint for licensure may be handled.

I would far prefer efficacy trials, and if they were to be done I would prefer them to be really

targeting pneumococcal pneumonia in whatever best way they could target pneumococcal pneumonia within the limits of our diagnostic capacity. But the idea that urinary antigen may be more useful or is more useful in adults makes that a little bit more feasible than in young children. However, I'm fairly pragmatic and see that as a huge barrier to the sponsor's interest in taking this forward. And my sense is that we really will likely have to come up with something that will be less stringent. And because of all that has been discussed, I think that whatever we can do to maximize the immunologic parameters and maybe adding colonization so that it isn't just OPA, but OPA -- of whether avidity further studies are required in some subset. And considering the use of colonization, although it certainly can't be used as a true clinical endpoint, but it would certainly I think be very encouraging to all of us to see that there was a direct impact on colonization that mirrored the serotypes in the vaccine and was similar to that seen in pediatrics.

So I guess I'm coming around to the idea

of trying to come up with a way with as much stringency within the immunologic comparisons with perhaps colonization added to it. And anyway that so called superiority could be demonstrated or advantages maybe would be a better way of saying it; advantages such as the avoidance of the hyporesponsiveness or that we actually, which we won't be able to show, but the advantage of this might increase the level or the extent of the disease to include pneumonia rather than just IPD would be advantageous, I think, to the process.

I do think the reality is that in the clinical world they're probably going to continue to want and need and grasp on to the idea of that safety net of the 23-valent. And so at least for the beginning of this process of having a new conjugate available for adults, I think clinicians may still have a tendency to want to sort of top it off with the 23-valent. And for that reason the idea of documenting the interrelationship of these two vaccines I think I also believe would be important in the process of evaluating them in the licensure

process.

I'm, again, very excited about some more broad based protein antigen based vaccine of the future. And what occurs to me besides the agreement that efficacy studies will be required is that maybe some of these creative efficacy studies that Dr. Piantadosi was putting forth could be also considered, because this is a daunting task to look at pneumococcal pneumonia prevention for the protein vaccine, that maybe some creative discussion of those approaches for the protein efficacy studies would be very interesting. And I really think that those studies we need to take the opportunity to show that something is preventing pneumococcal pneumonia and not just IPD. And that would be a good point of having the bar at that level or at least having that be a goal of the evaluation.

And then finally I very much agree with a very stringent post-release evaluation of the effect of the introduction of this vaccine with studies such as Dr. Jackson's study or the ABC's indirect cohort sorts of studies.

CHAIR OVERTURF: I'm just going to make a point. I'm going to have to leave because I live in a third world state that only fly airplanes there on rare occasions. And Dr. Markovitz will end the discussion and take over as Chair.

Dr. Royal?

MEMBER ROYAL: Well, much of what I'm going to say it may seem a bit redundant, because it's already been mentioned, but again it is very important to develop an effective vaccine, especially in the elderly. And, however, when it comes to choosing between an efficacy study and a non-inferiority study, I think it's interesting that we're not using the term equivalency study, especially since the valancy of the vaccines are not equal.

My tendency is to lean towards supporting efficacy studies. It was mentioned earlier that there are creative ways for designing clinical trials. There are ways of new assays that are being developed to try to increase the sample -- the number of patients that can be pulled into those studies. We've heard a lot about that today. But we've heard a lot about the OPA

study. And some of that dealt with that assay in the context of killing, which means to in fact correlate with some efficacy for the vaccine. I think that that should be pursued and validated further.

It is exciting that a protein assay vaccine is being developed. Clearly one would need an efficacy trial for that to move forward. And the newer approaches for definitively diagnosing pneumococcal disease would be important to employ in assaying that vaccine.

With respect to invasive disease and whether a non-inferiority study would be adequate for approving lower valancy vaccines for trying to prevent that type of disease, we fall into the same sort of problem in that you end up preventing a subset of pneumococcal disease and eventually those caused by subtypes that aren't represented in the vaccine will start to emerge. So that issue has to be addressed proactively whether or not it's best to do a serial immunization with the conjugate followed by the polysaccharide or two conjugates, the first being what's currently available and subsequently with what

wasn't represented in the previous vaccine. Whatever the decision is, we'll find ourselves here at the table having the same discussion.

There was very brief mention early on during this meeting about other potential markers of response to vaccine, cytokine responses that seem to correlate at least with OPA responses and perhaps other clinical indicators of responses to the vaccine. When you think very little about the mechanisms associated that underlie an effective response, we're looking at a certain type of immune cell in the OPA and just what are some of the factors that are associated with effective killing or in the immunized patient with an effective response. I haven't heard much about what those are, and I think it would be useful to be able to get more information on that. Maybe the OPA assay might not turn out to be quite as useful as some of the more genetic cytokine or chemotactic measures in the context of other information.

Finally, with respect to the populations that we'd like to see targeted with the vaccine in the

elderly, another bit of information that would have been helpful, at least for me, would be to have known the demographics of the elderly population, whether or not the poor responsiveness is seem among all those that are vaccinated or whether or not there's certain subsets who tend to have a particularly poor response, and certainly there may be unique issues that could be targeted within those populations and that it would be important to know about.

ACTING CHAIR MARKOVITZ: Seth?

DR. HETHERINGTON: I'm going to be brief because of the time of day and restrict my comments to two topics. One was the question about whether an immunologic assay could be performed in lieu of a clinical trial.

I have no doubt that antibody is protective, particularly antibody against capsular polysaccharide. I have no doubt that the mechanism of action is opsonophagocytosis. There are doubts, however, with the OPA assay as described represents what happens in vivo. It used HL60 cells, the first line of defense in the respiratory tract is the

macrophage. Also it leaves open a doubt as to what results really correlate with efficacy and has a standard really been established, not just in the performance of the assay but the readout of the assay.

So I think there's -- and I've heard this going around the table, quite a bit of discomfort about replacing a clinical trial with the OPA assay.

Second is related, it has to trial feasibility which seems to be the primary driver for using a surrogate marker. There is a bit of disconnect, at least on the surface in saying, and I believe it is true, that the pneumococcal vaccine would have a big public health impact and then on the other hand we're saying we can't show that prior licensure. Perhaps there's a way to find some intermediate ground, but it should be measurable in some way as to what the public health impact is going to be. In that regard, although we don't discuss costs here, using the numbers that I saw today about estimated attack rates and estimated efficacy, and this could be off by an order of magnitude, but what I find on the back of the envelop calculation is a cost

to prevent one pneumococcal infection of somewhere in excess of a million dollars. So there is a reason to consider what the cost will be to society and whether or not we're willing to accept an in vitro assay as a measure of potential benefit.

If approval by an immunological assay is ultimately a path that the FDA wants to take, then it should be perhaps under an accelerated approval mechanism by which there are strong commitments post-marketing. And I think we've heard that from others. To do a large enough study to demonstrate clinical benefit and to particularly measure the impact of replacement disease.

The single most important lesson I learned today was that the impact of replacement disease could oblate, if not just severely decrease the efficacy of a vaccine long term. And I think that's something we need to address as we go forward and consider the implementation of these vaccines across very large groups in our population.

ACTING CHAIR MARKOVITZ: Thank you.

I'll go last then, and originally there

were so many good points raised I think in this discussion that I started out with the idea that I was going to quote various people who all had made good points. But then everyone made a good point, so I'm not going to go through everyone else's comments. But I would like to highlight a couple of my particular concerns.

One is I would like to echo the comments that a protein vaccine in the future which spans the different serotypes is something very exciting. And I would not like our decisions today to make it ultimately harder for a vaccine like that to come to market, other than perhaps if it can raise the bar in terms of true efficacy.

Second of all, in order to have a true non-inferiority study you have to have something to measure. To my knowledge, anything that's ever gone through our Committee before where non-inferiority was accepted in terms of immunology, there was a very well characterized and well accepted test which indicated immunity. We don't have that here with the OPA, in spite of multiple attempts to elicit true data that

really supports this as being the test. I haven't been able to do that in questioning the manufacturers.

I would echo what Seth said and to some degree what Pam said, although taking a little different spin on it, which is that I certainly agree that antibodies are going to be utterly crucial to this process. But the question is really does this test measure those antibodies. So I have a lot of concerns about doing a non-inferiority immunologically based study.

And then the second and obviously crucial point here which if it were different, might allow us to get around some of these concerns is that we just don't have enough serotypes. And again, in the past when we've approved vaccines based on non-inferiority, there's never been a drop in the number of serotypes that I'm aware of. So dropping the number of serotypes that I think is very potentially quite dangerous now, I think as Gary noted before his departure for the third world of New Mexico, that it is true that we might not need 23 serotypes in there in order to have really good coverage. But I think we

need more than 11 or 13. So I think that that's going to be a very important consideration.

Lastly, I would like to say that I am very enthusiastic ultimately about, contrary to what it may sound like, I am very very enthusiastic about the idea of applying conjugate technology to this issue. And so I would like to, hopefully, see clinical studies. But if we do end up having clinical studies, I would hope that the FDA and the manufacturers would show a fair amount of flexibility in how those studies would be done. We might have to rely more on studies in other countries or specific groups, or anything that is deemed ethical. And I think a number of my colleagues have made some very good suggestions about how to approach that.

And so, I think that's the end of my comments.

Do we have any other comments people need to make before we adjourn? Anything that you need to mention before we quit?

Christine?

Okay. Meeting's adjourned. Thanks,

everyone.

(Whereupon, at 4:39 p.m. the meeting was adjourned.)