ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

June 24-25, 1998 Meeting

Verbatim Transcript

SNIDER: We'd appreciate it if everyone would take their seats. We're already a little late. Mr. Chairman?

MODLIN: Good morning. My name is John Modlin. I'd like to welcome everybody to the June meeting of the Advisory Committee on Immunization Practices. As our first order of business, I'll turn things over to Dr. Snider for his usual announcements.

SNIDER: Good morning everyone. I'd like to welcome everyone to this ACIP meeting, and particularly those who had to travel, especially those that had to come in late at night to attend this meeting. We want to welcome several people. Dr. Paul McKinney, if you could raise your hand. He's from the University of Louisville, my alma mater. He's the liaison representative from the Association of Teachers Medicine. I also want to acknowledge Steve Sepe. Steve is representing the National Vaccine Program Office for Rob Breiman, who is out in Arizona taking care of Native Americans. Also Tom Vernon is here somewhere I think. Tom is here representing PHARMA on behalf of Gordon Douglas.

Dr. Suzanne Jenkins—Suzanne, where are you? She's coming later. Suzanne works often with CDC on veterinary medicine matters and she will be the liaison for the National Association of State and Public Health Veterinarians. Specifically, she's coming for the rabies recommendation discussion. I also want to welcome back Georges Peter, who you all know. Georges is today representing the American Academy of Pediatrics for Larry Pickering, but he'll be joining us in October as the liaison representative for the National Vaccine Advisory Committee. For those of you who don't know, our representative to the National Vaccine Advisory Committee is Mimi Glode.

At each of the members' places should be a yellow folder. I see it, I think, at every spot. If you have not done so, you need to sign the enclosed letter, which is a waiver letter, and return it to Gloria before you can participate in the meeting. This is to tie up all the paperwork related to conflicts of interest, which we'll have more about later on. CDC is currently moving to a new e-mail system. At the moment, I still haven't been able to retrieve my e-mails from last Wednesday. So it's a difficult transition. If you have my e-mail, or Gloria's or Kathleen's on your machine, you'll have to delete it. You folks have probably been

through this kind of thing before, but you have to delete it and add it back on your global mailing list or your individual mailing list. Otherwise, you'll get an error message that says it was not delivered.

We are, just for your information, attempting to transmit more and more material electronically since it is a lot more efficient and a lot faster. It gives us better turnaround when we need comments. So if you happen to have e-mail access now and you didn't before, please let Gloria or Kathleen know your e-mail address. Now you may want to pay particular attention to the following message because it breaks tradition, and that is that this auditorium is going to be renovated starting October 1st—in fact, Auditorium A, Auditorium B, all the classrooms underneath. So this whole area is going to be undergoing renovation. That is obviously going to create some major problems for meetings at CDC, particularly meetings that are this large.

So this is the last meeting we're going to have in this auditorium and it's estimated that it'll take two years. So we've looked for a new home. The October 21st and 22nd meeting, we will meet at the Atlanta Marriott North Central Hotel. The address and information on that hotel is a blue sheet at the back of the room. If you do choose to stay at the hotel, you're going to have to call that hotel directly and tell the hotel you're attending the ACIP meeting to get the appropriate rate. The meeting dates for 1999 have already been set. There's a hand-out in the back of the auditorium for this. Next year's meetings will be February 17 and 18, June 16 and 17, and the October 21—I'm sorry—October 20 and 21. So that's February 17 and 18, June 16 and 17, and October 20 and 21.

Now in March, the ACIP Charter was renewed. The ACIP members will note that there's a copy of this charter in your notebooks. In this Charter, the Executive Secretary or my designee has given authority to temporarily designate *ex officio* members as voting members if they choose to do so. That only takes place unless there are less than seven members not qualified to vote due to a financial conflict of interest. We'll get into this a bit more when Kevin Malone makes his presentation a little bit later. Also with regard to involvement of the public in our discussions, I think those of you who have attended a number of meetings know that the Chairs of this Committee have made, I think, successful efforts to incorporate public comment during our discussion period of a particular topic. Of course, we have a restricted time frame in which we conduct business.

However, we have had, as you know in the case of polio for example, specific requests to speak on specific topics. When we have those, it's my view—and I think shared by John and others, both John Livengood and John Modlin—that it would be inappropriate for the Committee to go

ahead and take a vote on an issue if there are people who want to make a public comment about it. So we want to be sure that we have the public comment relevant to a particular topic before the Committee votes. So in addition to—we're not going to stop doing what we've previously been doing, which is allowing people the opportunity to make comments during discussion periods—but we have gotten formal requests for people to make comments. Therefore, we are going to have people making public comments. We have to restrict the amount of time that they have available to make those comments so that we can get through our agenda and conduct our business.

For certain topics, we will allow—in this case, Lyme disease—public comment before votes are taken on Lyme disease for example. If in the future people have, or even at this meeting people want to make public comments about a specific topic and get that registered before the Committee takes action on a particular matter, then you need to let Kathleen or Gloria know. We need to have a sign-in sheet so that we can keep track of this so that we can schedule these kinds of things and be able to move through our agenda in a reasonable and timely fashion.

We have three members whose terms expire on June 30th. We want to thank all of them. Dr. Barbara DeBuono assumed the term of a member who resigned and has been reappointed for a full term. So she's been with us for several years and we want to thank her for her work on the Committee. She's going to be late today. In fact, she's officially served since January of 1993. In addition, Marie Griffin has spent the last year commuting from California and stayed with us even through her sabbatical. We want to thank you, Marie, for your work with us. Dr. Fernando Guerra is actually going to stay with us awhile. Even though his term expires, he's agreed to serve an additional two more years on the Committee.

As most of you are aware, the nomination process is a long one and sometimes gets rather complicated. We've added two additional members to the Committee, but those members have not yet been appointed. So we appreciate it, Fernando, that you've agreed to stay with us awhile during this transition period. For those of you who may be new to the ACIP meeting, the folks at the tables draped in blue are either representatives of the program, but the majority are the regular Committee members. The folks at the maroon-draped tables are either liaison members or *ex officio* members from other government agencies. The liaison members are from a variety of professional groups that have an interest in immunization issues and we're glad to have them.

Because it's important for us to hear all the comments, we do have microphones up for people in the audience who don't have access to a

microphone at their table to be able to speak. We do ask you please to use those microphones so that we can record what you say. We are making full recordings of the meetings and full transcripts of the meetings. This came about as a result of some Congressional requests and we're honoring those requests by having full transcripts of the meetings in addition to the minutes, which you're all familiar looking at.

I don't know that I need to go over where all the restrooms are. There's restrooms down the stairs underneath this room. There are restrooms close to the entrance in Building 1. There are restrooms down this long hall over into Building 16. There are restrooms close to the elevators. If you have questions about where they are, ask Gloria, or Kathleen or someone of the rest of us who are on CDC staff and we can direct you. The cafeteria is directly behind John and myself in Building 16. So if you go down the hall toward Building 16, you will encounter the CDC cafeteria for better or worse. There is a snack bar too. It is in, actually, the first long hall over in Building 1. Again, the easiest thing might be to ask someone if you want to get to the snack bar. It's not hard to find, but giving directions is not so easy.

Dinner this evening is at the 57th Fighter Group, which is sort of on the campus of the Peachtree-Dekalb Airport. Dining will be casual. You should have some green forms to record what your choice of entree is. If you will mark what you want in the way of an entree and return it with the cost of the dinner to Gloria Kovach or Kathleen by noon, you will—if you need a menu and you don't have one of these green menus, you can see Gloria or Kathleen. We will leave from the lobby of the Emory Inn at 6:45 p.m. So lots of housekeeping, but I think that's all of it for the moment. John?

MODLIN: Thank you, Dixie. Let me add my own welcome to Dr. McKinney and to Mr. Sepe for joining us, and also to Georges Peter and Tom Vernon, who are of course familiar figures here. Just a couple of very quick announcements. I understand that the influenza statement was published on May 1st. There are copies of this recommendation in the back of your notebooks. The MMR statement is at the printer and hopefully it will be published if it hasn't already. As I recall, I made the same announcement back in February.

CORDERO: It's on the WEB.

MODLIN: It's on the WEB so it must be that it's been published then, which is good news. Let me reiterate Dixie's admonition for everyone to speak directly into the microphone, including those making comments from the back of the room. Let me also reiterate that I intend to keep things as much to schedule as I possibly can. It's in the interest of everyone here that we stay on schedule and finish on schedule. So I will again

apologize in advance to anyone who I get a little bit short with for running over time. With that, I'd like to start with introductions by members of the Committee, by the *ex officio* members and the liaisons. I think we'll start with Dr. Le, go around the blue table first, and then we'll ask the liaison members to introduce themselves. When you introduce yourselves, I wonder if you would also go ahead and make your disclosures with respect to potential conflicts of interest. Chinh?

LE: Yeah. I'm Chinh Le, the Chair of the Infectious Disease Subspeciality for Kaiser Permanente, Northern California region. In terms of disclosure, Kaiser Permanente has some vaccine studies with Merck, Wyeth Lederle and SmithKline Beecham. I do own some stock with Merck and used to own some stock with Aviron, but no longer.

GRIFFIN: Marie Griffin, Vanderbilt University. I'm currently on an Endpoint Monitoring Committee for Merck.

CLOVER: I'm Richard Clover from the University of Louisville. I receive grants from Merck and SmithKline. I've received honorariums from Connaught and Merck.

HELMS: Chuck Helms from the University of Iowa. I have no conflicts.

LIVENGOOD: John Livengood, National Immunization Program, CDC.

CORDERO: Jose Cordero, National Immunization Program at CDC.

MAWLE: Alician Mawle, National Centers for Infectious Diseases, CDC.

FLEMING: I'm David Fleming, the State Epidemiologist of the Oregon Health Division, and I have no conflicts.

GLODE: Mimi Glode from the University of Colorado and I have no conflicts.

GUERRA: Fernando Guerra from the Department of Health in San Antonio. We've done some work for SmithKline Beecham, for Merck, for MetImmune and North American Vaccine—either vaccine field trials and/or some consulting work and received honorariums from both SmithKline Beecham and MetImmune.

SNIDER: Dixie Snider, Associate Director for Science, CDC.

MODLIN: Okay. John Modlin from Dartmouth Medical School. I own a small number of shares of stock in Merck and I have participated in educational programs supported by Pasteur-Mérieux Connaught. Why don't we begin with Dr. Santos?

SANTOS: Jose Ignacio Santos, National Immunization Council of Mexico.

MARCHESSAULT: I'm Victor Marchessault from the Canadian National Associate Advisory Committee on Immunization.

MCKINNEY: Paul McKinney, Department of Medicine, University of Louisville.

GALL: Stan Gall, University of Louisville, representing ACOG.

SIEGEL: Jane Siegel, University of Texas, Southwestern Medical Center, representing HICPAC.

ZIMMERMAN: Rick Zimmerman, University of Pittsburgh, representing the American Academy of Family Physicians.

HALSEY: Neal Halsey, Johns Hopkins University, Chair of the Committee on Infectious Diseases for the American Academy of Pediatrics.

PETER: Georges Peter from the Brown University School of Medicine and also representing for this meeting the American Academy of Pediatrics.

SCHAFFNER: Bill Schaffner from Vanderbilt University, here on behalf of the American Hospital Association.

GARDNER: Pierce Gardner, State University of New York at Stonybrook, representing the American College of Physicians.

VERNON: Tom Vernon sitting in for Gordon Douglas of the Merck Vaccine Division, presenting PHARMA.

GLEZEN: Paul Glezen, Bayer College of Medicine, representing the Infectious Disease Society of America.

TRUMP: David Trump, representing the Assistant Secretary of Defense for Health Affairs.

GRAYDON: Randy Graydon, representing the Health Care Financing Administration.

SEPE: Steve Sepe, National Vaccine Program Office.

HARDEGREE: Carolyn Hardegree, representing the Food and Drug Administration.

RABINOVICH: Gina Rabinovich, National Institute for Allergy and Infectious Diseases.

EVANS: Geoffrey Evans of the National Vaccine Injury Compensation Program.

MODLIN: Geoff, thanks. Let me mention, as we will discuss this in some detail a little bit further, that ACIP members who do have a potential conflict of interest have made it known. I should note that all members, regardless of conflict, may participate in discussions of all issues provided that full disclosure of a potential conflict of interest has occurred. However, persons with a direct conflict of interest cannot vote on any issue that's related. With respect to the VFC Program, members with financial conflicts of interest must abstain from voting on VFC resolutions. Since a conflict may also appear to be present if such a member is allowed to introduce or second a VFC resolution, ACIP has adopted a policy that prohibits a member with financial conflicts of interest from introducing or seconding a VFC resolution.

With the paperwork out of the way, we'll begin this morning's meeting with a number of updates. The first is a summary of a very interesting meeting that took place earlier this spring at NIH on evaluating the role of vaccines in infectious diseases and autoimmune disease, particularly insulin-dependent diabetes mellitus. Dr. Gina Rabinovich is going to give us an update on this meeting. Gina?

RABINOVICH: Thank you for the opportunity to present the meeting summary of the workshop entitled *Evaluation of the Possible Role of Vaccines and Infectious Diseases in Type 1 Diabetes Mellitus* held in Bethesda on May 14th and 15th. The purpose of the meeting was to gather a multi-disciplinary group—including folks with expertise in diabetes, infectious diseases, pediatrics, vaccinology, immunology, epidemiology, public health and vaccine safety—to evaluate publicized hypotheses linking vaccination and diabetes in the context of changing concepts of epidemiology, as well as diabetes.

Reflecting the broad multi-disciplinary group put together and also the concern that this data be evaluated on behalf of the public sector, the parents of children with diabetes who were very concerned with the press that was received in late February, as well as the parents of young infants. It was a broad range of co-sponsors for the meeting, which included all the usual initials: NIH; Allergy Infectious Diseases, as well as Diabetes and Digestive Diseases; CDC, which included presentations from both the National Immunization Program and the Diabetes Epidemiology Group; the National Vaccine Program Office; the U.K. Department of Health, whom we collaborated in trying to untangle this for about three years; the Food and Drug Administration; HRSA; as well as co-sponsors that brought together the unusual gathering including the Juvenile Diabetes Foundation, the WHO-Global Program on Vaccines; the IDSA Vaccine Initiative; the Institute for Vaccine Safety at Johns Hopkins University; the Children's Vaccine Initiative; and the American Diabetes Association.

The purpose of the evaluation and the way it was conducted was a review by experts of the current concepts and gaps in areas of diabetes, neonatal immunization, developmental immunology and autoimmunity. There were two formal presentations that represented independent reviews. One was a formal independent evidence-based review by the Cochrane Collaboration that had been requested by the U.K. Department of Health—the collaboration with the inter-agency group. The second was a presentation of an independent review by the Institute of Vaccine Safety and Dr. Neal Halsey.

The rationale for the hypothesis, the kind of data that had been gathered in the literature, really was more than recent over the past three years. I believe Walter Cronkite had added diabetes to the potential adverse events of immunization as early as 1982. It was one of the topics that was reviewed by the Institute of Medicine's vaccine safety projects to review the adverse consequences of pertussis and rubella, and did not find a whole lot of data on that. The role of infectious diseases in diabetes per se has been hypothesized for many years with some intriguing data, specifically for rubella and a variety of the enteroviruses.

There are some data from actually a variety of investigators on genetically-susceptible mice and rats. The non-obese diabetic mice with very little provocation themselves develop diabetes, and so are a useful model perhaps to evaluate what kinds of factors can modulate that immune response. There have been ecologic analyses presented and published of diabetes rates and national immunization schedules in several selected countries, and several secondary analyses of vaccine trials that afforded the opportunity for a long-term follow-up with the caveats that come along with secondary analyses of data where that is not the primary end point.

A couple of things that I need to mention about diabetes since this is a probably a group of vaccinology experts rather than diabetes experts — the current consensus right now is that, what I was taught, was juvenile diabetes is indeed largely immune-mediated and is now called Type 1 diabetes. Evidence from different parts of the world indicate a 75-fold variable incidence and reported increasing rates over the past decade or more. A lot of evidence that specific antibodies to pancreatic cells and isolate cells precede disease in more than 90 percent of cases—sometimes from nine months to many years prior to onset of diabetes per se. So the thinking about how to evaluate anything that would cause diabetes has to take this incredibly long lag time, as well as the now availability of specific antibodies that need to be considered.

What was very clear was the emerging data over the past decade on strong genetic influences. Susceptibility and resistant alleles may be

necessary and sometimes sufficient, and environmental factors including infectious diseases in general are multiple and likely non-specific. The animal models for diabetes, as I said, with the NOD mice and the BB rats, develop diabetes as they do when observed with nothing done to them at a very high rate. The nature of this animal model for diabetes is that MHC class II genes are essential for expression of the disease, and that T cell function is essential for disease. These are thought to be parallels to how the disease expresses in humans.

A number of antigens and other non-specific stimuli—food, environmental conditions, change in lighting, temperature—prevent or modulate the rate at which diabetes expresses in these animals, especially in the short-term. So for any experiment that's conducted on these animals, all these factors need to be very carefully controlled. There are a number of things about this model that are unknown. What is the primary autoantigen? How do class II genes prevent diabetes mellitus? In reality, what the limits to interpretation from what we're learning from the animal models can be extended to humans.

There are a number of questions we discussed—the pathogenesis of diabetes for about four hours that I will not attempt to summarize— but there are a number of questions that were highlighted as things that are important to answer which really are unknown in terms of juvenile onset or immune-mediated diabetes. How do the genetic factors determine risk? What are the non-MHC genes that impact on the measurement of genetic risk as defined by a twin pairs? What are the specific environmental factors that can initiate or suppress a factor that may have already begun or a risk factor be present for genetic factors? What is the primary autoantigen? How to prevent or suppress autoantibodies for diabetes? Can insulin therapy delay diabetes mellitus, which is something that's actually being tested right now in some small trials.

A significant amount of time was spent discussing one study that was presented as evidence. This was a previous Hib vaccine trial in Finland where it was possible because of their—I was told they're the best VTU in the world because of their unique system to be able to link vaccination data in a very detailed fashion from the randomized cohort of the Hib trial at infancy or at two years of age to the diabetes registry and find per individual what the rate of diabetes subsequently was. The review of these data by one investigator concluded that there was an association—Drs. Klassen and Claussen. The review of the vaccine trial by the Finnish investigators who collected these aspects of the data did not attribute the rise in type 1 diabetes rates in Finland to differences in the timing of childhood vaccination in the study.

There were a number of methodologic flaws and suggestions made as how these differential analyses could actually be compatible if the right rules were applied. The conclusion of the workshop was that there was indeed a consensus—although not unanimity; the investigators who really believe in this hypothesis I don't think were convinced, but I think there was clear consensus in the room reflecting a diverse group who would love to find a way to prevent diabetes and if a vaccination did it, so be it—that existing studies in humans did not indicate an increase in type 1 diabetes attributable to any vaccine or to the timing of vaccine administration.

A number of promising areas of research in diabetes and infectious diseases were defined. Studies that may provide additional data in humans are ongoing, specifically the University of Colorado DAISY study, which is looking at a cohort of siblings of diabetics in a control group in about 800 children; and the Centers for Disease Control and Prevention Vaccine Safety Data Link, the study which has a project ongoing on these. Each time I've attempted to summarize this to the group, I've asked what are the next steps. I think in the process right now is submission and publication of the reviews, and other analyses that were presented. We are preparing a workshop summary for the workshop itself. That should be submitted and available through peer review in referenceable articles. That will join the kind of literature review, when one reviews the data, the kind of evidence that is out there. Both the Cochran and the Finnish analyses have been, as far as I know, submitted.

There were a number of suggestions made for improvement—a logical analysis of available data. These indeed were reasonable approaches to go and do ecologic analysis as sort of hypothesis-generating, but the right statistical and analytic approaches needed to be taken and would need to be rigorous. A number of gaps in knowledge were defined with a call for basic and epidemiologic research. For example, there was a discussion called the Pediatric Framingham. I've heard this discussed by different groups, but you know, a birth cohort with detailed serum, cell bank, environmental history, antibodies, et cetera, to rapidly evaluate different hypotheses that are rising to explain the variation and increasing trend in diabetes; the development of a humanized mouse that develops diabetes mellitus, the requirement of human T cell assays with the specificity and sensitivity that's required, and further explanation of prevention approaches to autoimmune diseases. For example, super antigens and the role of cytokines mediating potentially was the environmental risk.

I've attempted to summarize what was really not just one workshop, but several that have been held and several in-depth reviews that have been held. The conclusions were not evident at the beginning of the

workshop. They really arose from—were challenging to come to, but I think based on the available evidence and the strength of the evidence, the group felt very comfortable that the conclusion that immunization was a safe and effective tool that should continue, but that there were areas of research that should also precede, was a valid one. Thank you.

MODLIN: Thanks. A very nice, concise summary of what must have been a very interesting meeting. Are there any—we have time for one or two quick questions or comments. Neal, you were there.

HALSEY: No. I would just reaffirm a couple of the points that Gina made. They are also similar to the conclusions that we made at the Institute for Vaccine Safety. I think it's most important to emphasize that the consensus certainly of both meetings was that there is no evidence that any vaccine has increased the risk of diabetes in humans at all or in animals. This is perhaps a precursor to a number of other things that will need to be looked into. If you listen to the Internet and people concerned about vaccine safety, there are rumors that continue to surface with regard to causal relationships between vaccines in various diseases.

The diseases are being targeted are those for which we do not understand the pathogenesis. Diabetes is but one of those; there are many others. Many of them are autoimmune or immunologically-mediated diseases. So I think that we will need to have further investigation into the pathogenesis of those diseases and these issues with regard to other vaccines won't go away. It is encouraging to me that there may be some things that can be done immunologically in high-risk populations that might modify or decrease the risk; it's possible; it's conceivable. I think many of us believe that there may be some vaccines that might actually have a benefit in that direction, but again to re-emphasize, there's no evidence of an increased risk of diabetes from any vaccine that's been introduced in any country of the world.

MODLIN: Other questions or comments? Thanks, Gina.

RABINOVICH: Thank you.

MODLIN: Next on the agenda is an update from the Food and Drug Administration. Dr. Hardegree?

HARDEGREE: I'd like to thank the group for the opportunity to update the ACIP on some activities that are underway at the Center for Biologics since the last ACIP meeting in February. I cannot comment and will not today on activities related to FDA as a whole except in one area. First, I'd like to

let you know about a major review that our scientists in our research program underwent by a distinguished group of scientists consisting of regulatory scientists, people from academia, industry and government over a four-day period in February.

The report was presented by the Chair, Dr. Les Bennett, to the Science Board in May. There was a strong support for the need for a regulatory program in biologics; that that regulatory program have a mission oriented research program. This report can be found in CBER's WEB page. I would ask that you may want to take a look at this. The report emphasized the need for capable scientists to address the complex issues of products being developed with the new technologies and to remain capable of assessing vaccine safety in the future. I think the emphasis was indeed on making sure about the vaccine safety in particular as far as the group in this room is concerned.

Next, I'd like to let you know about an approval that I think many of you as infectious disease investigators and physicians will want to be aware of. On June 19th, FDA approved the first monoclonal antibody directed against an infectious disease, RSV. The monoclonal is directed against the A site on the fusion protein and can be given by intramuscular injection in contrast to the currently available polyclonal antibody for the prevention of RSV. It has been studied in infants with bronchopulmonary dysplasia and in infants with a history of prematurity that is less than 35 weeks of gestation. The manufacturer of this product is MetImmune.

As you heard from Dr. Modlin, the recommendations for influenza have been published. Since February, the WHO committees and our own vaccine advisory committee completed the selection of the strains of influenza which should be considered for inclusion in the coming year's vaccine formulation. When we last met, only one strain—the B strain—had been considered definite. This year, the vaccine will have both a new H3N2 and an H1N1 strain included. The selections were affirmed at the March advisory committee and they are listed on this slide.

The March advisory committee of our own vaccine advisory committee also addressed the question of whether human volunteer studies of salmonella typhi could be justified. Such trials have been proposed in order to accelerate the development of new typhoid vaccines. Trials in volunteers have not been performed since the 1970s. The availability of new antibiotics to treat and prevent carriage has led to the request by NIH, WHO and a vaccine development center to consider such challenged studies again. The committee was supportive in proceeding with this model.

The May 26 and 27 meeting of this committee addressed several product-specific issues that I think are of interest to this Committee. The included licensed applications for a vaccine against Lyme disease, cholera vaccine live oral and an issue raised in a citizen's petition requesting the placement of a boxed warning on OPV. Tomorrow, there will be a full discussion of the questions that were raised by our committee on Lyme. I will not go into the discussion about those because I think they will be addressed by Dr. Elkins tomorrow. We were asked to address primarily the issues of the safety, the efficacy, citing in particular the age ranges which should be included in the labeling and in the usage.

These were focused around the types of studies that were done. The data on the efficacy after one year and two years; therefore, affecting the impact of whether or not you had to complete a three-series immunization schedule, and the need to question whether or not seasonal information should be included. I think it's to be noted that this Advisory Committee on two occasions had indicated that until information was available for the adult population, that study should not commence in children. Therefore, the group was not asked to address whether or not the product should be used in children. At the current time, as you will hear tommorow, there is not any information to relate to that.

In 1993, the Advisory Committee was asked to address whether or not efficacy trials in volunteers, as had been done at that time previously with live cholera vaccine given orally, could be used to support the efficacy of such products for use in populations in which cholera is not endemic; that is people who have lived in the United States possibly or traveling to areas where the disease may be endemic. At that time, they indicated that they felt that such studies could be useful, but no particular product was examined although one was used as an example. A licensed application has now been received by the Food and Drug Administration in which the primary data supporting efficacy was that from a challenged study.

A recently completed field trial in Indonesia did not show significant efficacy for the product; therefore, the committee was asked to address whether or not challenged studies could still be considered for the use of efficacy in the endemic population. The panel voted unanimously that challenged studies may suffice to demonstrate efficacy of cholera vaccine in U.S. travelers to cholera-affected areas. However, the panel found that the data submitted from the challenged volunteers that they reviewed was not adequate to support the approval and the efficacy of this product at this particular time. Areas of concern included the study design issue regarding randomization, controls and particularly sample size; immunity to El Tor infection; duration of immunity; issues related to

the need for boosters; and representativeness of the challenged population in terms of diversity and age.

The panel also considered that data to support the efficacy and safety of the product in children were inadequate at this time, and therefore, a minimum amount of time was spent on this topic. The third major topic discussed in this committee meeting dealt with the need for a boxed warning. As I indicated earlier, we had received a citizen's petition asking that a boxed warning be placed on all polio labeling. It was considered advisable to go to our advisory committee and ask for their opinion and their advice regarding this. No votes were taken, but the overall consensus of the participants at the table advised the agency that including a boxed warning in the OPV package insert would not be the most effective means of educating health providers, parents and vaccine recipients of the risk of VAPP.

It was emphasized that the labeling already includes statements regarding this in the precaution statements; that parents are given important information and vaccine information sheets that talk about these options, but it was apparent that people are not getting this message out. Our committee focused in a great part on trying to get FDA and CDC to provide additional public education and provider education—making sure that options are known and that we got out to our professional societies and advocacy organizations to talk about appropriate solutions. The agency continues to review the petition and its docket, and will respond according to the necessary administrative procedures.

Numerous committees within the Food and Drug Administration are having to address various aspects of issues related to transmissible spongiform encephalopathies, and the potential for their transmission in products derived from bovine and human sources. Since the last ACIP meeting, one of these committees—the Transmissible Spongiform Encephalopathy Committee that is chaired by Dr. Paul Brown—has addressed questions relating to tallow and additional questions about gelatin for oral or topical use. The committee heard presentations about the manufacturing and process controls, as well as new data on BSE in the United Kingdom.

Tallow derivatives are used in many food and drug products, such as those things like the polysorbates and the fatty acids that may be included in various materials. The committee voted not to change the restrictive policy that is already in place regarding the sourcing of these materials. Because they did not vote to make any change, no discussion was necessary regarding question two. The committee did vote to recommend a change in the policy for derivatives. That would again be the fatty acids, the glycerols—that type of product—because

the conditions that are used in the manufacture of these products were deemed to have been those that have been validated to show that you could inactivate the agents, such as things that might be models of the BSE.

The need to continue to address concerns on the TSE, such as those of CJD in blood products, has led some of the advisory committees within the agency and the department to continue to recommend a policy of withdrawals for blood products which have included a donor in a pool with a history of CJD, or if there was a family risk for CJD. We will hear later today about how this, along with other factors, has led to a shortage over the past year of some blood products, such as immune globulins and albumin. I don't want to go into any of those specific issue; however, I think it is important for this audience to recognize that some biologics, including some vaccines, contain licensed albumin from human sources as accipients, diluents or as part of the manufacturing process.

A consideration is being given by the agency on whether or not changes should be made in the way these products are labeled or whether any withdrawal policy should apply to any components that are utilized in the manufacture of these biologic products. The public health service agencies have not reached a consensus on these matters as it relates to any vaccine product, but I'm sure that we will be back to talk about this at a later date. Thank you.

MODLIN: Thanks, Carolyn. Any quick questions or comments about Dr. Hardegree's presentation? Neal?

HALSEY: Carolyn, given the number of withdrawals that have taken place, is there any effort to come up with a consensus as to what should be done in terms of counseling individuals who have received products that have been subsequently from the same lot of products that have been withdrawn? Will there be any federal government guidelines in this area?

HARDEGREE: Well, I would think that this is part of the process that's going on now in terms of what to do. We have not had to withdraw any of the vaccine-related products for such a purpose at this time. We are cognizant that in view of the number, that it is possible that it could occur. I think you're right that there needs to be some—I think the issue of risk is very minimal as recognized, but I think that this is why the discussion continues about this policy, Neal. It would be premature for me to comment on that.

MODLIN: Yes, Fernando.

GUERRA: Carolyn, the term "boxed warning" means what appears on the box itself?

HARDEGREE: No. It is a warning that is placed at the beginning of a label. It highlights certain things that may be deemed by the agency to be necessary to be included in a warning that is more prominent than is in precautions or contraindications.

MODLIN: Questions?

HARDEGREE: Thank you.

MODLIN: Thanks, Carolyn. We'll move on. The next update will be from the National Immunization Program, Dr. Jose Cordero.

CORDERO: Good morning. I have a combination of slides and two transparencies at the end. I hope that the projector is working and that we can get it—let's see. Okay. Thanks. Thank you for the opportunity to provide an update on the National Immunization Program. This morning, I will report on three items. First, the provisional data on vaccine preventable diseases—the surveillance of vaccine preventable diseases. Then I will cover briefly the most current estimates of immunization coverage at the national level. Then I will—well actually, there are four things. I will speak briefly about the budget, and finally, I'll show you some of the data, the most recent data, for the 1997 biologic surveillance on vaccine doses distributed.

In 1997, we had record or near record lows for vaccine preventable diseases. Measles is at an all-time low at 138. Although this is provisional data, 131 is about half of the previous lowest record. We do have some challenges in the control of vaccine preventable diseases. We continue to have outbreaks of pertussis and rubella continues to be a problem. We are having outbreaks, mostly among newly arrived persons from Latin American countries that do not include rubella in their immunization schedule.

Another challenge is not listed here and it is varicella. We continue to have a large number of outbreaks. We do not have a well established surveillance that's nationwide yet. We do continue to have deaths related to complications from varicella. That's about 120 deaths a year, about half of them in children. That's about an average of two deaths a week from a vaccine preventable disease and these are preventable deaths. Significant effort is needed to reach a level of community protection that can impact varicella mortality and serious morbidity.

The National Survey data for the last half of 1996 and the first half of 1997 show the highest national immunization coverage ever reported.

We achieved or exceeded at least 90 percent for three doses of DTP or three doses of polio, one dose of measles-containing vaccine, the same for Hib. The goal that we had for 1996 for hepatitis B was 70 percent and that was exceeded. It will be 90 percent by the year 2000. It looks like we may be able to get 90 percent by the year 2000. Varicella coverage is about 19 percent, but if you look here in the next slide, it looks like we've continued to have an increase in coverage. If we look at the last quarter of 1997, it went to 25 percent compared t the earliest quarter. There is a big range. Actually, what we have is that some states are being slow in implementing their varicella immunization activities.

We had in 1994, a significant increase in our budget. Our budget is actually divided into segments. On our grants, the goal for infrastructure for all the kinds of activities that need to be conducted and to have a complete immunization program; that's what's called a 317. Under that 317, there is another segment that relates to vaccine. What we're presenting here is data on the infrastructure for the operations. We went up to $228 million and continue to increase, but the states also accumulated a large portion of carryover. We did have a Congressional reduction in our base budget. Up to 1997, it was reasonable because we could cover the decrease with a carryover, but for 1998, that is not possible.

States on the average had a 38 percent cut from the amount spent in 1997. The $146 is what is on the current FY'99 budget and that would actually imply another reduction because of the lack of a carryover. The estimate would be about 38 percent also. In terms of vaccine, the good news is that the amount is somewhat level, but given the addition of varicella vaccine and the recommendations for adolescents and also the catch-up, we would be able to cover that expense only if we had a very modest increase in coverage for the new recommendations and the new vaccines.

Because of the decrease in budget, it's critical that we ensure that the core functions—those activities that are the most critical to ensure that we have control of all vaccine preventable diseases and that high immunization coverage are done. We have embarked on the process of identifying what are the core functions. At a previous meeting, I reported we were just beginning the process. We actually have had a series of meetings with partners from state, local health departments and volunteer organizations—a wide variety of partners. We have identified the core functions that are listed here.
Following developing this list, we have actually conducted about six site visits to states in trying to understand the cost in each of these items. Just to give you an example, we've done that with surveillance. On the average actually of seven states, it's that it ranged from somewhere

between 1.3 to 8.3 percent of the operation of the immunization program in the state. I think that's the last slide. We have received just a month ago the data on the biologic surveillance that gives us data on the distribution of vaccines. I'd like to just show you two transparencies—one on the progress on distribution of enhanced inactivated polio.

As you can see, there was a little over five million doses of enhanced inactivated polio that were distributed in 1997, indicating I would say, not in the statistical sense, but a significant uptake in the sequential recommendation. I think that to us is good news that the recommendation by ACIP, the AAP and the Academy of Family Physicians has been taken and put into use. Unfortunately, at the last hearing of the Vaccines on Related Biologic Products Advisory Committee—during the discussion about the box warning that Dr. Hardegree mentioned—a parent of a child recently diagnosed with vaccine-associated polio after receiving a dose of OPV, gave a very, very moving account of their anguish and the occurrence of their condition.

This was one year, nearly a year after the ACIP recommendation, and the AAP and the AFP recommendation. They reported not receiving the current VIS or the vaccine information statement at the time of the immunization. This to us suggests that the information distribution from providers and then to parents is less than optimal. This lack of information effectively denied these parents the opportunity to make an informed choice among the polio vaccine schedule. That is the basic underpinning of the polio recommendations of the three groups: ACIP, AAP and AFP.

To address this issue, NIP has sent letters to provider organizations asking for continued support to educate parents about the important options available when vaccinating their children against the polio virus. Specifically, the organizations were asked to train and educate providers regarding the risk and benefits of IPV, OPV and combination schedules; and second, to ensure that parents are receiving the most current vaccine information literature and verify that they have in their office an up-to-date version. These statements are available through state immunization programs. They're also available through the immunization hotline and they can be downloaded from our WEB site.

Finally, we would like to propose a comprehensive update on the status of the sequential schedule implementation at the October meeting. We also had some interesting data on the use of DTaP in the last four years. Basically, we have gone from a substantial use of DTP to basically, this is about half a million doses distributed in 1997. It's a very significant increase in the use of DTaP with a reduction on the use of

DTP-Hib. That again, I think is good news in terms of the use of acellular pertussis vaccines. That's the good news; let me give you the other side.

Over the past several weeks, CDC has received questions from Indiana and North Carolina on how to proceed in cases in which about 100 infants from each state had given TriHIBit for the primary series. This was done by several private providers. This vaccine has not been approved by the FDA for the use in the primary series to vaccinate infants. The combined DTaP-Hib vaccines are currently licensed only for use in children aged greater than fifteen months. ACIP did recommend its use for children twelve months or older who are unlikely to return for an additional visit.

The concern is that the use of the DTaP-Hib combination vaccine as the primary series may result in a reduced immune response to the Hib component. However, it is not clear how this will affect the child's susceptibility to invasive Hib. Currently, there is no apparent concern regarding the reactogenicity of DTaP-Hib and the means for immunization of infants in the primary series. FDA licenses its vaccines, and until they are licensed for younger infants, they should only be used for children twelve months or older.

To provide guidance to state immunization programs, CDC has consulted with FDA. We have developed a set of recommendations regarding subsequent immunizations of children that had received immunizations inappropriately. Actions to be undertaken to identify the reasons, establish procedures to ensure that all children receive immunizations according to the ACIP recommendations, and track subsequent compliance with recommended schedules. Providers of vaccines should be educated regarding the current ACIP recommendations for immunizations and ensure that compliance of the recommendations is monitored. In the case of a child who receives TriHIBit in the primary series, CDC in consultation with FDA recommended that the decision to reimmunize a child with Hib vaccine be based upon the number of prior doses of TriHIBit given at the primary series. Thank you. That's the end of my report.

MODLIN: Thank you, Dr. Cordero. Questions or comments? Let's start with Fernando.

GUERRA: Dr. Cordero, if you could go back to the slide that shows the increase in uptake of the enhanced IPV. The total of number of doses there has decreased significantly, at least those that are distributed. What is the explanation for that going from about 23 million doses down to maybe about 17 or 18 million combined?

CORDERO: I think that that has to do with catch-up and that actually there are the 20—it's about close to the number that we should be using for the set of vaccinations.

MODLIN: In all likelihood, we'll include polio on the October agenda. Dave?

FLEMING: Jose, the 38 percent reduction for the states that you mentioned is going to be. . .

CORDERO: I'm having trouble hearing you.

FLEMING: The 38 percent reduction in funding for states that you mentioned is going to result in basically an all-consuming activity at the state and local level for the next year as far as people trying to figure out how to preserve at least components of their program. Could you talk about what kind of reductions are anticipated at the federal level and whether or not that's going to influence the program's ability to support ACIP deliberations?

CORDERO: We have had some decrease in the operations. We don't expect that that will affect the ability to support ACIP, but part of what has happened in terms of the broad operations of NIP is that there are specific expenditures that are being directed and that overall is decreasing our total operations budget. That's about, I think, the way I can describe it.

MODLIN: Bill, you had a question?

SCHAFFNER: Yeah. Thank you. I had a question and a request. My question was asked by Fernando. So the request of Dr. Modlin and Dr. Cordero is perhaps in the future in addition to this fine presentation, we might add a segment on the occurrence of vaccine preventable diseases and vaccination coverage in adolescents and adults.

MODLIN: Good suggestion.

CORDERO: I'd be delighted. Thank you. That's a topic I would love to talk about.

MODLIN: Paul?

GLEZEN: Going back to the education on polio vaccines, I have not seen a parent education form that includes specifically the reversion to virulence of OPV on a regular basis for type II and type III. I really think that that should be included in the statement so the parents understand it. I think they would—this would encourage the parents to be much more cautious about diaper changing and things in babies if this was included. I think it should be.

CORDERO: Thank you.

MODLIN: Thanks, Paul. Maybe that's something we can focus on at the October meeting. Chuck?

HELMS: This data I presume reflects primarily utilization habits in clinics and doctors' offices, and the choice of the clinic or the doctors' offices to which type of vaccine to use. Is there data on demand from the public—what parents are wishing?

CORDERO: I'm not familiar with any data—at least our NIS does not have that— but we do have in the north of Atlanta, we've been monitoring acceptance of the schedule. Actually, this is in Cobb County. John, if you would ensure that I'm doing the correct number. This is a group that is about a third White, a third African American and a third Hispanic. These are public clinics. What I recall is something that about a third of the children are actually getting the sequential schedule. John, is that in the ballpark?

LIVENGOOD: That's why I think it's more than a third. What we really have right now are data on choices about the first two doses. We don't really have data on the third. Our data from that setting is very much consistent with—this is about 30 percent here of all polio is IPV. If you say that it's all going to the first two doses, it's between 60. In our own clinics, we're looking at 70 percent of parents are choosing to begin with IPV in those settings. We'll have a whole lot of data on this from multiple different studies that we'd like to discuss in October, but I think that this was just a good introduction to the overall topic.

MODLIN: Alright, Georges.

PETER: Well, a comment with respect to the polio. In several post-graduate courses where I spoke, of which in fairly significant attendance, an informal poll—a show of hands—on how many had adopted the sequential. The figure indeed was between 60 and 70 percent and it does seem to be increasing. In some respects, that's a pretty good figure given the controversy that preceded this change, but we have to continue. The second point is a question related to varicella vaccine. I know several states are or have passed regulations for requiring varicella vaccine for school and day care entry. I wondered to what extent the program is encouraging states very actively to adopt regulations within their states. I've talked to Tom Vernon. I think there are about eight states now that have them on the books, but still, eight states isn't very many given the data that you've presented on lack of utilization of this vaccine.

CORDERO: Some states have, like Massachusetts just passed a regulation for varicella vaccine. Obviously, I think that every state is trying to determine whether the benefit of including or going through the process of adding the regulation is greater than the complications of opening to a new regulation given the environment which we are at right now—such low disease and the concern about, for instance, the community in terms whether there should be more parental choice.

MODLIN: Jose, while we're on the question of varicella vaccine, how do you define or how did you define varicella vaccine coverage for the 25 percent figure? Are these two year olds? Are these twelve year olds?

CORDERO: Yes. This is the standard National Immunization Survey. These are 19 to 35 months old. That's what we have routinely done since 1994.

MODLIN: Thanks. Dixie.

SNIDER: With regard to polio, I just wanted to make it clear that there are actually two points. The first is of much greater concern. As Jose said, at the VRBPAC meeting, there was a report from the parents of an infant who got VAPP who indicated that not only did they not get a vaccine information sheet prior to the vaccination—which would've helped them make a choice—but the sheet they got was after the immunization occurred and it was the older version. So the issue of making sure that people are able to make an informed choice is an extraordinarily high priority, I think.

The second issue, of course, is people adopting what we regard as the preferred schedule, which I think is never perhaps going to be 100 percent because people will have their own reasons for choosing one or the other schedules, which is fine as long as they're appropriately informed in doing so. So we were very concerned and have heard from John Salomone about two other cases. Apparently, similar things have occurred. So I think there's some urgency in trying to get the information out about the fact that there are options, and getting that information to parents prior to immunization taking place; and secondly then, of course, monitoring to see whether people are adopting the preferred schedule, or all IPV or all OPV—how that's breaking out.

MODLIN: Thanks, Dixie. One last quick comment. Phil?

HOSBACH: Phil Hosbach from Pasteur-Mériuex Connaught. We recently completed a study in about 1,000 new moms. One of the disturbing things that we found with regard to polio information is that about 60 percent of them didn't realize there were two vaccines available. When we did inform them in a balanced way about vaccines and the three alternative schedules, more than 80 percent of these mothers chose a

sequential schedule. So that's information that we hope to publish very soon.

MODLIN: Thanks, Phil. We need to move on if we can. Jose, thanks very much. We sure appreciate it. It was an informative update. The next presentation will be by Dr. Geoffrey Evans, National Vaccine Injury Compensation Program.

EVANS: Good morning. I'll just mention that Mr. John Salomone, who Dixie referred to, is the vice chair of our commission and is the head of a group known as Informed Parents Against Vaccine Associated Polio. It was in that regard that he brought the petition to the FDA and VRBPAC meeting. Let's begin by looking at the monthly statistics sheet which most of you have. The program is basically in a steady state, receiving about nine claims per month. The changes covering Hib, varicella and hepatitis B last August really have not significantly increased the numbers that are coming in. Of course, there's eight years of retroactive coverage for any new vaccine added and a two-year window to file for the older claims. So I'm sure we'll be seeing more activity, especially with hepatitis B, which the program has received a fair number of calls over the past couple of years wanting to know when it would be included.

Going to adjudications, we're about 98 percent of the way through with the pre-1988 case load. The awards are over $900 million to date and there's a little bit over $1.2 billion in the trust fund. This pays, of course, the post-1988 claims for vaccines that were administered today. I'd like to spend the remaining time talking about some possible future changes to the program and begin by talking about some of the legislation that has preceded today. The Advisory Commission on Childhood Vaccine, which is the oversight body for the program, met this past June. It meets four times a year. It has been reviewing for the past year a series of proposals—legislative proposals—that grew out of a subcommittee that was looking at various process issues.

These meetings would bring in consumers and petitioners, attorneys, representatives and others with ideas and comments about a whole range of issues. From this effort, I'm going to present some of the possible legislative proposals that may eventually be coming from the department. The first, what I thought I would do is just talk a little bit about the changes that have occurred up to now and how they've come about. The original law was, of course, the National Childhood Vaccine Injury Act of 1986. The first series of legislative changes that occurred in 1987 and 1990 really were just the initial set-up kinds of things, such as the funding, setting up a trust funds, court procedures and so on.

More importantly, in 1990—not more importantly in the sense of getting the program going, but in terms of something that was unique to our program is that we began to work with Congress, industry, the American Academy of Pediatrics and others in terms of effecting process improvements based on the experience that we were gaining over time. Those series of amendments and changes are seen in the 1991 to 1993 legislative actions there. Very important of course was Ober of 1993, which have provided the permanent reauthorization program and also added a mechanism for adding new vaccines.

I should mention that any vaccine that's recommended by CDC for routine administration to children is eligible to come into the program once an excise tax is voted by Congress to cover it. Then in 1995 and 1997, we went through the regulatory process, rule-making and effected changes to the Vaccine Injury Table twice: the first set in 1995 involving pertussis and rubella vaccines; and the second, measles and tetanus among others, and also put a provision in there that any new vaccine recommended by CDC would be automatically added to the table again pending the rule-making change. That included adding—we added at that point or specified that Hib, HepB and then later varicella would be added. So that was all part of that 1997 rule-making.

Of course, once this was published in 1997, we needed an excise tax for those three new vaccines. That came with what was called the Taxpayer Relief Act of 1997. I've broken these down into various categories. The first category is a series of legislative proposals that have been considered by the commission. Most of these have actually been voted unanimously. The first one actually came up at the meeting in June. This was not quite as clear a vote. It was five for and two against with two abstentions, but this has to do with the interpretation of the law having to do with a factor unrelated. As things stand now, most claims allege a table injury—a condition that's listed on the Vaccine Injury Table—and should it be evident in the record, and should the time frames be satisfied. Then unless there's a definitive alternative cause or what's known as a factor unrelated, then the claim is eligible for compensation.

There have been some instances in which genetic disorders may not be clearly defined for a while. Up until recently, there was not a clinically defined biologic marker for it. Because it was not clearly defined as its cause, the court interpreted the fact that it was considered idiopathic in terms of its specific cause to still not be clear enough to rise to the level of effect or unrelated. So we were put in the position of having to prove the cause of the cause. Of course, that's impossible in many situations. So this clarifies what we believe to be the Congressional intent; that when you have a child or an adult who is clearly diagnosed with a non-vaccine related disorder even if the precise cause is not known, the fact

it fits into a category, such as a genetic abnormality or a structural abnormality, that this should be able to rise to that level of weight. That's the provision that we propose to be added to the statute.

The second has to do with the statute of limitations. As things currently stand, petitioners have three years in which to file an injury claim and two years to file a death claim. Yet at the same time, any new vaccine or any new condition that's added to the program is given eight years of retroactive coverage with that two-year window I talked about. Another fact is that if you have a claim that's filed for a child. Let's say the experience is a DTP-related injury, a two-month or four-month shot, and they're filing when the child is a year of age or just a little bit older. Of course, it's too early to really know what the eventual developmental outcome will be. So this allows petitioners additional time to assess what the child's current condition is and give them that opportunity to have that at the time that they file a claim. So this would extend it up to six years, which actually goes along with other statute of limitation standards.

The final is more of a technical limit and having to do with the fact that Congress, when they enacted the law, put a $1,000 threshold in order to eliminate frivolous claims. Petitioners have to show $1,000 of unreimbursable expenses in order to be legally sufficient. That, as it turned out, has precluded some otherwise eligible claimants from pursuing their action in the program. This would allow them to file even if unreimbursable expenses are less. Moving on, this would simply eliminate the requirement the Advisory Commission meets four times a year. Of course, this is more than other laws and regulations for other advisory committees, and allows us to bring it in line with some of the other schedules for other committees. This is something that the commission had no problem with.

This came up more recently with a member, actually John Salomone's group, expressing the desire to be a member of the commission. As things stand, the three general public members, two of whom are to be legal representatives of the Vaccine Injury Child, this would preclude actually a vaccine-injured adult from being a member. So this would open up the possibility of having that kind of insight into the experience that people could bring to the commission. For those of you that participated with us, helped us through the rule-making process for the two sets of table changes, you well remember that it took nearly four years for each effort. This would reduce the public comment period from a half a year to just a couple of months and eliminate the requirement for a public hearing. It actually turned out during the Section 313, the second effort, that when we had a public hearing, no one showed up for comments. So this is something that we thought was appropriate.

The next set of changes has to do with issues that I'm sure the ACIP doesn't deal with very often—the process of compensation for attorneys' fees and costs. A couple of the issues yet have been very important for petitioners and petitioners' attorneys, such as the interim payment of cost. There's a situation in our program. If a claim was brought by an attorney in good faith and reasonable basis, that even if the compensation is denied to the petitioner, the attorneys' fees are paid. If the petitioner is eligible, it is only at the end of the entire process that the fees and costs are paid to the attorney. This means if they have to front them at the beginning, some attorneys will not participate in the process. This can be a great financial burden to the petitioner if they have to pay it, so this was something that was thought to be—that would relieve that situation assuming that the petitioner has already been judged to be eligible for compensation.

There's actually two parts to the adjudication process: the eligibility determination, and actually the final assessment of the damages and the compensation. The next two have to do with specific elements that are covered in compensation, such as family counseling expenses —not for the injured party, but the family cannot be covered by compensation. This, by statute, would be added and needs to be added by statute. The cost of providing a guardianship which ensures the regular fiscal management of an annuity, for example, and a pay-out over a lifetime, the cost of setting that up would not be passed on to the attorney or to the petitioner.

The final is a little bit more controversial, just having to do with just the technical way the checks are issued to petitioners and attorneys. That's going to be addressed further at the next meeting. Switching gears for a moment, this is now going to be what is going on in Congress. This is legislation that the program has not introduced or the Secretary has not introduced, but yet it's pending currently. We're very pleased with the first one because this would reduce the excise tax, the current excise tax, which is 75 cents per dose down to 25 cents per dose. This was introduced by a House, Ways and Means Committee member. It has very wide support, including both the Speaker and the House Minority Leader. There's also a companion bill in the Senate that's been introduced. It also seems to have bipartisan support.

We are quite optimistic that this actually may make it through this year and be passed into law. This, of course, would reduce the price of vaccines. Currently with the three additional vaccines that were added to the program and even with the revision to the excise tax down to 75 cents, the excise tax monies coming in have actually increased from $140 million annually to $170. With the $1.2 billion in the trust fund, obviously, this is money that we don't need; it's excess money. This is an important change to the program.

There is another bill that we were a little surprised to see. It turned out that there was an amendment added this past spring to the Internal Revenue Restructuring and Reform Act. I'm sure you've heard about that. The amendment was inserted by a member of the Senate, and also noting, I'm sure, the ACIP vote that occurred also because they referred to CDC in the Senate committee report. So the status at present is that the conferees have to meet and reconcile their differences between the Senate bill which has this amendment, and the House Bill which does not and how that would affect—I mean, if it's put into place, it's not clear to me how that affects when the tax goes into effect, but certainly, once CDC makes the recommendation, it would certainly facilitate it being added to the program. It very well could be added right at that point since it's already been passed into law. I think I will stop there. Are there any questions?

MODLIN: Actually, we just have time for just one or two. Mimi?

GLODE: I just wondered of the 39 awards that have been compensated at an average of about $1 million each in 1998. Could you just grossly tell me just the distribution of what vaccines were involved? I mean, were most of those DTP or do you know?

EVANS: Three-quarters of the vaccines in the program were DTP, so my guess would be that those were DTP-related encephalopathy—these according to the legal conclusion and those that represented the cost of annuities, those kinds of things.

MODLIN: Okay. Thanks very much, Geoff. It's appreciated. Finally, an update by Mr. Sepe from the National Vaccine Program.

SEPE: Thank you very much. Let me provide a brief overview of some of the activities in the NVPO. I must say that the brevity of my presentation in no way correlates with the amount of activity that's been going on in each of these areas. The first activity I'd like to update you on is the influenza pandemic preparedness plan. The NVPO has been coordinating the activities of the working group on influenza pandemic preparedness and emergency response. This is a group of influenza experts from public and private sectors. Their continuing work began in 1993 to ensure that the United States is prepared to respond to an influenza pandemic.

The working group as we reported previously has created a comprehensive conceptual influenza pandemic preparedness plan that addresses the steps needed to be taken to minimize the impact of a pandemic. At the request of the Secretary, detailed subplans in the areas of influenza research, surveillance, vaccine production and

development, vaccine delivery, anti-viral agents, hospital and clinical guidelines, communications and costs have been drafted by subgroups of the working group. The NVPO is now reviewing these drafts and will be consolidating them into an updated plan. We hope to review several key elements of that plan, including the role of the ACIP, and the response to a pandemic at your next meeting.

Another major activity that we've been involved with is coordinating the development of a vaccine safety action plan, which will help direct efforts to ensure the optimal safety of vaccines. As you know, the Office of the Secretary approved and released the task force plan for safer childhood vaccines about a year ago. This plan—this new vaccine safety action plan—will hopefully provide a blueprint for the implementation of the task force report. It's being developed by an inter-agency group, including representatives from the NVPO, the Office of the Secretary, NIH, FDA, CDC and HRSA. So we're hoping to have a draft prepared in the next few months. A smaller working group composed of members of each of the agencies involved has been put together, co-chaired by NVPO and FDA, to actually put pen to paper and come up with a draft plan in the near future.

There are two Presidential initiatives which are ongoing. The first I'd like to mention is a Presidential initiative on race. It's a $400 million initiative which has not been funded yet, but it's an initiative to help close the gaps in racial disparities. The Department of Health and Human Services has selected six areas for focus. They include breast cancer, cardiovascular disease, infant mortality, diabetes mellitus—there's one other—and immunizations. Dr. Cordero and Mr. Toman from HCFA are co-chairs of the working group to put together the plan for immunizations, which will have two components: one for adult immunization and one for childhood immunization.

So that's an activity which has a very short time line. Plans are due at the beginning of August. If funded, money would become available this next fiscal year, fiscal year 1999. As I said, it's a $400 million proposal, $30 million of which will go to community development programs for each of the six areas selected. So there's a possibility of additional funding for adult and childhood programs at the community level. We'll hear more about this as time goes on. The second activity, which is kind of an unofficial Presidential initiative, is the development of a plan—a national plan—for registries. At a ceremony about a year ago, last July I believe it was, the President directed the Secretary to develop a national plan for infant immunization registry systems.

Under the auspices of the National Vaccine Advisory Committee, a subcommittee, a working group of the National Vaccine Advisory Committee has been put together to develop the plan The working

group is staffed mainly by the National Immunization Program and thus far has held three, what we're calling, town hall meetings to look at issues surrounding the development of registries. There are four specific areas that are being looked at. They include technical considerations, monetary considerations, privacy and confidentiality, and recruitment and retainment of providers. Meetings have been held as far as Houston, New Orleans and San Francisco. The fourth meeting will be here in Atlanta in mid-July.

After the four meetings, the work group will sit down and put together the plan using the considerations and the information that was gained from each of these meetings. That will hopefully be drafted in the next few months. I think there's a September or October kind of preliminary deadline for putting that together. The final thing I'd like to tell you all about is that the National Vaccine Program Office, in coordination with the WHO, CDC, NIAID—here's a new one on me, the International Union Against Tuberculosis and Lung Disease—the American Thoracic Society and the American Lung Association are coordinating or hosting a conference on TB vaccine development and evaluation.

I've brought a number of these with me and they're on the back table if you'd like to take one. We have hundreds, thousands more. So I'll manage to make sure there's a box of them back there so you can all take one. The meeting is scheduled for August 26th and 28th in San Francisco. It's a three-day symposium to provide an overview of the public health implications of TB; to explore candidate vaccines and identify barriers and solutions for vaccine evaluation; the role of the United States and international vaccine manufacturers, academia, government agencies and non-government agencies; and stimulating TB vaccine research will be explored. The conference will examine and facilitate the implementation of the universal strategy for TB vaccine development and evaluation. Thank you.

MODLIN: Thank you. One question. Chinh?

LE: Yeah. I'd like to ask you about the first item—the influenza pandemic preparedness. Are there representatives of major health insurance and managed care in that group? I'm thinking mainly that, you know, the private sector, and academia and the scientific community can come up with all kinds of plans and new vaccines and so on, but the brunt of the epidemics will be on the providers.

SEPE: Right.

LE: Our last more severe outbreak of flu in California taught us that we were not prepared at all in the private sector to take care of them because HMOs had been cutting back a lot of beds, cutting out staff and so on. I

think involving the major insurer so that when the pandemic comes, there are enough beds and enough staff to be prepared.

SEPE: The simple answer is yes.

MODLIN: Thank you. Pierce, quickly.

GARDNER: I guess I'd like to hear a little bit more about the relationship of the National Immunization Program and the National Vaccination Program. The similarity in names breeds some confusion and particularly with regard to my interest in adult immunization issues. Now Dr. Cordero's presentation was entirely pediatric-focused; you mentioned influenza. I guess in particular, whose job is it to fret about pneumococcal vaccine rates which are well under 50 percent for a disease that we consider the largest cause of mortality of any of the things you worry about.

SEPE: I guess the National Vaccine Program Office is responsible. It was created, by the way, by the same legislation that created the Vaccine Injury Compensation Program. We're responsible for coordinating federal activities in the vaccine area. We don't deliver vaccines; we don't provide vaccines; we don't provide any money for infrastructure development. We don't provide any money to state health departments. So our major activity is to keep the federal agencies talking and involved in the sort of over-arching issues that involve all the agencies and not just one in particular. The National Vaccine Program Office has been responsible for developing an inter-agency, inter-departmental actually, adult immunization action plan, which has been approved by the Office of the Secretary and released about a year and a few months ago.

That action plan is forming the basis for the adult component of the Presidential Initiative. So the National Vaccine Program Office has taken on adult immunization as a specific area. As has the National Vaccine Advisory Committee has taken on adult immunization as a specific focus in terms of helping to develop some broader inter-departmental plans to hopefully reduce the coverage differences between the pediatric and adult populations.

SNIDER: I know we need to move on, but just to remind folks that the National Vaccine Program Office came to CDC when there was a downsizing in the Office of the Assistant Secretary for Health and came into my office. Perhaps the simplest way to look at it is ACIP is looking at specific vaccines and how they might be used—combinations of vaccines, adverse effects of particular vaccines—whereas, the National Vaccine Program Office and the National Vaccine Advisory Committee in particular are looking at a much bigger picture or issue. How do you get vaccines in the pipeline, out of the pipeline? How do you establish

policies that are conducive to better vaccine uptake? As I say, much bigger picture items. Chuck has been on the NVAC, so you may want to talk to him if you want a lot more detail, Pierce.

MODLIN: Thanks, Dixie. We do need to move on. Thank you very much, Mr. Sepe. At the last meeting, several members requested that we as a Committee put on the agenda for today's meeting a discussion of potential financial conflicts of interest and how they relate to votes that the Committee need to take. So we've invited Mr. Kevin Malone from the Office of General Counsel here to lead us in this discussion. Kevin?

MALONE: Kevin Malone with the Office of the General Counsel here at CDC. I'm going to go over the financial conflicts of interest policy that CDC has as it applies to the ACIP. Then I'm going to briefly mention a couple of recent revisions to the ACIP Charter related to voting that Dixie mentioned earlier. Then we'll open the floor to discussion and questions that anybody might have. As you can see, this is a very straightforward issue and since lawyers are known for doing small print, I thought I should start with a little small print. Unfortunately, it's an issue that I'm hoping that I'll make it straightforward in this presentation, but I think it actually is a little less straightforward than even I think I can make it.

There's a federal conflict of interest statute at 18 U.S. Code Section 208 that prohibits federal employees from having financial interest in matters in which they work. Those include special government employees, which ACIP members and other advisory committee members are also considered to be. Federal advisory committees though inherently have members who have potential or financial conflicts of interest because members are chosen for service based on their expertise in the areas in which advice is sought by the government.

Congress has recognized the need for service by these experts on federal advisory committees despite the potential for conflicts of interest by providing for waivers of the conflicts of interest prohibitions under Section 208 when "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved." Given the departmental interest in fully utilizing the expertise of all members, but also sensitive that the financial interests of the members have implications for the credibility of both the committee and the department given particularly the immense financial impact of VFC decisions, CDC adopted a waiver policy that assures not only technical compliance with the provisions of Section 208, but also fulfills the spirit of the law by taking into account the issue of the appearance of financial conflicts of interest.

Thus, the focus in our disclosure on the existence of the relationship rather than the amount of the interest. Some considerations then in focusing specifically on ACIP were one, ACIP has a very unique role. Under the VFC statute, it is given the operational role to determine the vaccines that will be used in the Vaccines For Children Program, and any comparable role a federal employee would be required to divest all interests that are related to that. Conceivably, Congress was aware of the interests of the Committee and decided that it would be appropriate to place this in the Committee, and certainly we will allow those interests to exist. Second, there is the advisory role; however, I might point out that the advisory role that the Committee has is very intertwined with the VFC role. So we essentially treat them identically except for the narrow point that John brought up earlier regarding the introduction of resolutions and seconding of them.

So ensuring the integrity of the Committee, we do that we hope by maximizing the utilization of expertise and minimizing the potential for the appearance of the conflict of interest and accomplish this by doing two things. One is allowing full discussion by all members in exchange though for public disclosure of the relevant financial interests. Therefore, the people in the room, the general public, the fellow ACIP members and the government are fully aware and can take into account any kinds of interest that a person may have. Then we only restrict in a specific way, and that is restricting voting to only those members who do not have financial conflicts of interest.

What interests are covered? Current direct financial interests—specifically, there is a timetable of twelve months for purposes of reporting your financial interests on the 450 Confidential Information Form that you file with the department. Beyond that, the twelve months are not really that applicable except for purposes going to the $1,000 honoraria cap that exists. We require that you take into account honoraria received from a single entity during the past year. If you divest an interest though, once that interest is divested, you are free to vote on that matter. Whose interests are covered? Your interests are, those of your spouse, your dependent children and other interests are attributed to you; the financial interests of any organization in which the member, spouse, minor child or general partner serves as an employee, a general partner, an office or director, or other fiduciary capacity.

For an example, someone may be the chair of a committee that receives financial backing from a vaccine manufacturer. We would consider that to be a fiduciary capacity for purposes of this matter and would consider that to be a conflict of interest. Lastly, if you are negotiating for prospective employment or you have current arrangements for prospective employment. What interests are

covered? Employment, stock ownership, contracts, consulting relationships, receipt of grant funds, including those sources of funding for vaccine studies. In looking at the various direct financial interests, we concluded that we could narrow it somewhat and were able to declare two specific interests to be essentially *de minimus* interests. One of those is limited honoraria, which currently we apply an annual limit of $1,000 per reimbursing entity—not including travel expenses. The idea behind that is that the agency has an interest in encouraging participation in scientific forums. Anything that we can do to encourage that given the minimal ongoing interests that an employee will have by simple attendance at the limited number that $1,000 cap would give, we think makes it reasonable. However, as one caveat or one condition for waiving limited honoraria, we do require that you disclose receipt of honoraria and travel expenses for the past twelve months. The second area is uncontrolled university interests. Obviously, universities are quite extensive institutions that we don't really expect your average member to have any idea of certainly the investments of the university. So we have decided that uncontrolled university interests are so far removed from the individual that they will not be considered to be included.

We would include in that what are called pooled income sources. I understand that some departments will pool all the grant funds that come in and then will dispense it as part of people's salaries, and yet they have nothing to do with a particular grant. In that instance where you have a source of income from a pooled income source, disclosure would not be required. To show the opposite of that then, what are controlled interests that would not have a voting waiver? One would be serving as the PI for a study; another would be serving in line management over individuals who utilize the grant funds; and lastly, a member is responsible or instrumental in obtaining the funds that are at issue.

Given those interests then, the scope of waivers that we have given to ACIP members, as I mentioned earlier, there is a full waiver for all Committee discussions and only voting restrictions for those members who have conflicts of interest. That restriction by the way applies to any vaccine that a manufacturer has because again, as I mentioned earlier in the talk, we are interested in the relationship more than the specific issue that you may be working on with a vaccine manufacturer. Again, the ongoing conditions for waiver are that you file a confidential 450 form which is reviewed by the government in deciding whether or not to issue the waiver, and lastly, that you disclose all relevant financial interests at ACIP meetings.

There's been some confusion, I think, about what the voting restrictions actually are. I'm hoping that maybe this will clarify it a little bit.

Members must abstain on votes where they have current direct financial interests. The interest is not waived for purposes of voting; that is it's not limited honoraria or uncontrolled university interests, and the issue under consideration as a potential for significant financial impact. That would mean primarily something that's geared toward the introduction of a vaccine into particularly the VFC Program, and also the inclusion of particular numbers of doses or lowering numbers of doses. Something like contraindications, we would consider would have such a minimal impact on the financial situation of a vaccine manufacturer that we would consider that a *de minimus* interest that would not have to be considered.

The other things I want to mention briefly are, as Dixie mentioned, the ACIP Charter has been amended to allow for voting by the *ex officio* members when there is not a quorum of qualified regular ACIP members. We considered any number of possibilities for how to open up the Committee to additional members to vote on issues, in particular, VFC. I maybe should go back a little bit. The genesis of this is that there has been some criticism of some of the VFC votes. For example, there was one that was a 2 to 1 vote. So we have looked for various ways to see if we could expand the number of voting members.

We looked at the various issues that I just went over. One thing I might mention is that we are interested in getting any kind of input you might have today on whether raising the honoraria limit might have any effect on that, and whether that would be a good idea or not. We finally came down to deciding that the *ex officios* would be the most appropriate people. As federal officials, they're already prohibited from having conflicting financial interests. In addition though, they also have the broader perspective of the entire operation of the Committee because they're ongoing participants as opposed to individuals who might be brought in from the outside. I understand that the FDA frequently does bring in folks from the outside to serve as temporary members. We did consider that and rejected that because of our concern that for someone to be brought in to vote on a particular matter, the odds are that they would be brought in for the very reason that they have a strong interest in that matter. They would likely have the same kinds of conflicts that other members have.

The final thing is that the Charter currently provides now for seven members to be qualified to vote in order for a VFC vote to take place —in order for any vote actually to take place. The seven came from that the Committee is currently chartered to have twelve members although two of them have not been appointed yet. The seven though, however, are already in effect. Whenever then there are not seven qualified voters—that is people who are capable of voting because they don't have financial conflicts of interest—present in the room, at that point, the

Executive Secretary has the option of empowering the *ex officios*—all of the *ex officios*; there are seven of those—to vote on that particular matter. That's my presentation if anybody has any questions.

MODLIN: Kevin, thank you. Dr. Glode?

GLODE: Thank you very much. If only the world were black and white instead of gray. Who makes the decision whether or not the apparent or true conflict of interest exists enough that the person should abstain from voting? Is that something—is that a decision you make before the meeting and that's incorporated in the waiver or does the person themselves decide whether they abstain?

MALONE: Well, we've been discussing that some recently because I think there has been some confusion. As you pointed out, unfortunately, this is very gray. It can frequently be very difficult to come up with a decision about whether a particular interest actually is a conflict of interest. What we've done in the past is through the letters themselves, we have pointed out interests that we consider to be conflicts and we've had informal discussions with members. One of the things that we've discussed recently is perhaps being a little bit more direct in advising the members about precisely what those might be, perhaps even changing the way that we present it. Getting your permission, for example, to have the Executive Secretary read out the conflicts at the beginning of the meeting might be one option.

We would actually welcome any kind of comment people would have on how those interests should be disclosed. Just one other comment though to the extent that you feel that there is confusion in your own life, I would suggest that you contact me or Dixie Snider. We have a small group of folks that get together and review the 450s and those same people would be glad to look at your particular interests and advise you accordingly.

MODLIN: Dave?

FLEMING: I have a question about whether or not the information that you presented around uncontrolled university interests in your mind would also extend to uncontrolled governmental interests. Many of us, and I would be an example, are governmental employees. I'm an employee of the State of Oregon. There are many potential parts of state government that may or may not be engaging in grant activities with vaccine manufacturers. Should I be applying those same criteria that you listed for the university interests to my job, or alternatively, are there a different set of criteria?

MALONE: Well, we're open-ended on that, but our general approach to that has been that we do not consider state health department employees to have financial conflicts of interest unless it—again, this is an area of gray. I think if you were specifically working, if your group was specifically working on a matter that was being financed by a vaccine manufacturer, it would be problematic and we would want to know about it. The broader interests of the department as a whole—and certainly every department is involved in vaccine delivery programs—we feel would not be covered. The Office of Government Ethics by the way has put out some regulations that define some of these areas. They point out that being a purchaser of a product is not considered to be a conflict of interest.

MODLIN: Dixie?

SNIDER: Just back to Mimi's point because I know she's participated too in VRBPAC meetings and MCA meetings, and know how the conflicts are read there. The company is not mentioned, but it's obvious. Because the way the VRBPAC works is that you have on the schedule dealing with a particular vaccine on a particular day. So it's just implied; whereas, our meetings on a particular vaccine, our discussions, you know, might go on for eighteen months or more before we finalize a recommendation, which makes it more problematic when we're talking about, you know, six or eight different vaccines during the course of a meeting to do the kind of announcement that is done at FDA. That's why Kevin in essence said that we would have to have your permission because your 450s are supposed to be confidential.

So what I personally would favor and would like your reactions to is to be able to read out at the beginning of the meeting who would be able to vote on what issues for us to help you, you know, by making those determinations. Sometimes we may have to consult with you before the meeting. So that's one way to deal with it in a similar way, you know, to FDA and tell you in essence, you know, which issues you can vote on or you cannot vote on, but it would require that we have your permission, you know, to disclose that particular information. By going around the table, we're not violating your privacy because you're telling us yourself, you know, what your conflicts are.

The other thing I wanted to say is with regard to the consultants, you know. We looked at, again, the FDA model of bringing those people in, but I think the fact that again, we talk about a particular vaccine for multiple meetings makes it much more difficult for us to try to use that model on an ongoing basis for additional voting members if we need them then it does for the FDA because they run into some of the same problems, but they're solved by having the consultants there. That's why we thought the *ex officio* route might work much better for us, more

efficiently for us than trying to figure out how many consultants we're going to need to garner a quorum to vote on any particular issue. It would be a shame to have somebody come in, you know, for the meeting to vote on one issue and go back home, you know, after, you know, a one-hour discussion. So those are some of the things going on in our minds.

MODLIN: The trick is to bring in a consultant who is an unconflicted consultant. That's not the reason why you bring a consultant in necessarily. The reason is you bring them in for their advice and not because of the fact that they're unconflicted. In fact, that's what happens at the FDA. It's when a consultant is brought in and once a decision is made to bring them in, then their financial interests are looked at and they are told whether or not they can vote, but they can still participate in the discussion.

MALONE: Can I just add a couple of points?

MODLIN: Yes. Sure.

MALONE: One is on the disclosure form itself. The 450 is a very frustrating form. All of use that same form too and it's very difficult to even figure out what it is that you should be disclosing. One of the things we've talked about is producing a supplementary form that would more explicitly lay out the types of issues because certainly if we're going to be in a position that we have to be announcing these interests, we would also need to feel a little bit more confident, I think, that everything actually is being reported.

CLOVER: I think it would be helpful if you could specify who is eligible to vote and who is not prior to the vote for two reasons. Number one, as has already been mentioned, there are a lot of gray areas and your advice on what those gray areas are would be helpful. The second is there are frequently multiple manufacturers of a given vaccine and I may not have knowledge of who all has that vaccine in the pipeline, and I may not know a conflict exists because of that. So any assistance you could give to us with that regard would be helpful.

MALONE: One point of clarification there is, if a vaccine is not licensed, we do not consider it to be a conflict yet—frankly, mainly just for practical purposes. The second thing is currently, we read out a list of the manufacturers of a vaccine prior to a vote to alert the members regarding their personal interests.

CLOVER: That's news to me because I withheld voting on potentially licensed vaccines because of interests or potential conflicts of interest.

MODLIN: Does that mean those of us who own stock in Wyeth can vote on the rotavirus vaccine?

MALONE: Well, there are particular instances that, again, the gray comes in here; that where the cart is before the horse, maybe you might want to reconsider that. Certainly, I would encourage anybody that wherever you feel that there is a potential for a conflict, I would be more inclined personally to recuse myself from voting. This is a very liberal policy. I don't think it appears to be to many people, but we allow absolute discussion by all members. FDA has an incredibly complicated process that they go through.

A lot of it's geared toward actually excluding people from even being in the room, much less discussing based on the total numbers of dollars that they have invested and their net assets as a percentage of the thing that they're working on. We tried to come up with something that we hope is easy to understand, and yet does preserve this appearance that the interests that folks have in vaccine companies are not unduly influencing these very important votes. These are really unique votes. Unlike FDA, this is an operational group for purposes of the VFC votes. That's a very significant point.

SNIDER: I think, John, it would be helpful to us to get a sense of two things and people may want to provide other input as well. Dr. Clover has already expressed his view, but I'd like to hear more from the Committee about their willingness to have us make the decisions and make the announcements, which would mean, of course, that they would, you know, have to provide us some additional information as was indicated. There is—FDA does send out a form that's a little different than the 480 asking you specifically about interests in certain manufacturers. So we could develop a similar type form, you know, to find out if there are any relationships—financial relationships —between individuals and the particular companies whose products are going to be discussed at a particular meeting, and find out the nature of those things because if there are honoraria, for example, you know, they are not going to—and less than the $1,000 per manufacturer is not going to be a reason to recuse a person from voting.

The other issue is whether people do feel that changing from $1,000 to $2,000 or $2,500 based on whatever the going rates are today would make a big difference because I think our feeling is—obviously, we don't want to jack it up too high—but our feeling is that once we've gone above 0, we're open to some criticism anyway and we ought to make that, you know, it shouldn't be a large amount of money, but it ought to be reasonable based on whatever the current rates of honoraria are.

MODLIN: Right. Mimi?

GLODE: Well, I'm equally as concerned as you are about the 2 to 1 votes. I'm worried that people actually are not voting when it would in fact be appropriate for them to vote. The example I'll use, but I don't know the details, is Dr. Le, whose giant organization, giant HMO/university/ state, has vaccine contracts. Again, I don't know whether any of your salary comes from those, or if you're the principal investigator or whatever. Obviously, on that you would have to, but if your giant HMO is involved in vaccine trials, to me, if that's not part of your daily activity and you're not funded by that, then would—but it seems to me that you do abstain and I'm not sure you need to. Maybe a legal opinion would be you didn't need to if my statements were correct; I don't know, you know. So I'm trying to get away from the 2 to 1 votes. I've already heard four people this morning that sounds to me like won't be voting on a lot of issues, so we're down to three or four, you know.

MODLIN: Fernando?

GUERRA: Yeah. I certainly agree with the suggestion that it would be very helpful if you could help us go through the process of whether or not it is a potential conflict for us. The questions that I have for you, Kevin, are, you know, I think it's more than just the financial disclosure and issues around voting. On the integrity side of it, you mentioned that you should try to minimize the potential for appearance of conflict. Does that include such things as social interaction with representatives of companies that we are going to be discussing their products? Does it also include issues related to how we deal with the media when, you know, we are certainly approached on any number of instances related to, you know, some recommendations that specifically are targeted to some of the new vaccines and/or participation in just discussions with consulting firms for some of these companies? What are some of the parameters that you could help us with?

MALONE: Well, I can tell you that we actually have had discussions about whether or not we needed to expand it beyond a consideration of merely financial interests; that if there is a strong working relationship with a manufacturer that doesn't have any dollar, whether that is an interest that should at least be disclosed and whether or not it would be disqualifying. We've not really come to any conclusions on that. I would welcome any kind of comments on that.

SNIDER: Yeah. Just to elaborate, I think our concern though is not social interactions or comments around scientific issues and so forth, but there have been some situations in which questions have been raised when a member is or appears to be in a position of promoting a particular manufacturer's product even though there's no funds being exchanged. I think our feeling is that we would like members not to

engage in that kind of activity. We think that compromises the Committee as well as the member themselves in terms of, you know, how effective they can be in talking with the other members of the Committee and giving the perception that they are truly open-minded about the issues. I think beyond those kinds of, you know, promotional activities—the other kinds of activities I think are much more problematic in terms of trying to make a decision that would be negative because all of us, including those of us here at CDC, meet with manufacturers and have, you know, discussions with manufacturers around a variety of issues: sometimes specific vaccines, sometimes the pandemic flu plan and so forth. So it's certainly not something we would want to proscribe or prohibit.

MALONE: That's actually one of the reasons why I think we allow full discussion given disclosure; that there are—it's a sliding scale, I guess, of contact between the manufacturers and members. This Section 208 law focuses specifically on financial interests, but given disclosure, people can take that into account. That largely legitimizes the process or makes it less likely that there will be illegitimate factors being taken into account.

MODLIN: I have a question for you, Dixie, and for Kevin. That is the determination of each individual voting member's potential conflict of interest on a meeting-by-meeting basis and on an issue-by-issue basis, it's going to be a considerable amount of work for someone here.

SNIDER: Yes.

MODLIN: The question is, maybe I should or shouldn't raise it, but who would be responsible?

SNIDER: We appreciate you raising it because it does—well actually, the person who's ultimately responsible is not here and that is the Deputy Ethics Counselor at CDC, who's Jack Jackson. Mr. Joe Carter usually signs off on his behalf. The reality is that people who are having to look at these pieces of paper and so forth, it's Gloria, and it's Kevin and it's me, you know. We all have other things we have to do. So it would be an additional burden for us. If we're going to do it, we're going to have to do an additional collection form prior to the meeting. We can't—we just don't have enough detailed information on the 450 to make those kinds of decisions that you would want us to make. So it would be additional work on your part to fill those things out. Once we had that information, we'd have to go through and make the judgments using the criteria Kevin has outlined for you. Then I would read it out at the beginning of the meeting.

Our concern is the same thing that, you know, Mimi has already expressed; that the ACIP process continue to be viewed as a credible process. We've really agonized about the fact that we've had these votes that where it really seemed quite ambiguous about what the Committee wanted to do because there were so many people who were not eligible to vote. Of course, there are people who've thrown that back to us, including vaccine manufacturers who've expressed some concern about that. We fortunately, thus far, no one has challenged us on the issues that have prevented the program from moving forward. We want to avoid having those kinds of outcomes in the future so you have a clear direction for where the programs ought to be moving and are not susceptible to people sort of putting an injunction on us, if you will. I don't necessarily mean that in an official legal way, but somehow stalling the process of moving forward because we didn't have a very convincing vote.

MODLIN: Expanding the Committee and on occasion allowing *ex officio* members to vote if necessary would at least partially address that issue.

SNIDER: Yeah.

MODLIN: It's not an ideal. . .

MALONE: One other way it gets addressed is cutting down on absenteeism.

MODLIN: Yes.

MALONE: That's a strong concern that we have. One alternative there is to allow phone participation when folks have a reason that they actually cannot be there, but perhaps they could at least participate in limited matters involving votes.

MODLIN: Good suggestion. I haven't heard anyone, that is, make any negative comments about this sort of arrangement in terms of—Dave?

FLEMING: This isn't a real negative comment, but I do have a little bit of an issue around what I understand is the proposal for *ex officio* voting. My understanding of what you're proposing is that if there are less than seven members, that *ex officios en bloc* would be given the opportunity to vote. I'm perfectly fine with that. Taking a step back from a public appearance, that means that the *ex officios*, whenever they would be called to vote, would be in the majority because there would be seven of them voting and then by definition would be less than seven Committee members voting. I was wondering if you would consider the alternative, which was the selected designation of *ex officios* to get up to a quorum of seven.

MODLIN: Dixie?

SNIDER: Well, I hadn't thought about it, I guess, because I'm not sure how one makes the selection that, you know, this person or that person. I will say that we don't believe that all the *ex officios* will vote. I don't think I should say any more than that, but there are some *ex officio* members who feel that they would not be in an appropriate position to vote given what their agency might do or what have you. So how many *ex officios* will feel comfortable voting on a particular issue, I don't know, but it could be less than seven.

MODLIN: How do members feel also about the proposal to—the possibility of raising the $1,000 annual limit honoraria? In essence, $1,000 is two educational meetings. It would put you over the limit very quickly. As has been mentioned, this is a very arbitrary figure. Are there any strong feelings one way or the other about this number? Hearing none—Chinh?

LE: Actually, I wanted to kind of answer to Dave's comment. Actually, I feel somewhat relieved to have the *ex officio* members being able to vote at some point in time if we don't have a quorum because number one, I have full respect for their integrity, and their knowledge and so on. So I really feel very privileged to be able to participate in a discussion that I cannot vote on. I think that to me somewhat is enough. Hopefully, that perhaps what I say will influence the people who can vote for me if I cannot vote. So I don't have a strong feeling that the *ex officio* members may be more numerous than us.

In terms of my own example—if I wanted to use that as an example as Mimi brought up—with Kaiser Permanente for example, we have usually post-licensing studies, Phase IV studies. So the company does get some free vaccine for a year or so to do the study. As an ID person, I kind of am involved in it just to supervise the nurse, but I'm not a PI; I don't get any salary from that kind of funding. I don't get any honorarium and so on from that at all. So again, it's a little bit like the university part of it. On the other hand, I feel that well, if there's any resemblance of a conflict of interest, I feel comfortable not voting.

MODLIN: Neal, I'm sorry. Wait a second; let's respond to that.

SNIDER: Well, I think we need to—maybe Kevin and I both need to respond to that; is that I guess one of the things we're saying is that if a situation like that in which you have not received any financial compensation—it's a Phase IV trial in which the patients are the ones that are getting the benefit from getting free vaccine—then certainly we'd want that kind of thing disclosed, but there's nothing in the rules that he put up that would preclude you, you know, from voting. Now depending upon other

relationships that, you know, Fernando was alluding to, I mean, certainly the choice has to be yours because we can't know, you know, what kinds of relationships and discussions you've had with the company about the promotion of the vaccine and so forth.

It does—I guess the point I want to make is a point Mimi was making earlier; is that it hurts the Committee if we have people who could vote, who in good conscience could vote, who don't vote because then it makes it appear that the Committee is not constituted of enough objective people who can make a clear decision for CDC to go forward. This is the line we're trying to walk. While, you know, I'm not encouraging voting if a person's conscience bothers them because of that, I do want to be sure that you understand that there are negative consequences for the Committee for not voting. So I think one needs to have substantive reasons for not voting on issues.

MALONE: Can I just make one comment on Dr. Le's situation? Not to go into much detail, but we did specifically focus on uncontrolled interests at universities and did not directly consider HMOs. I don't know enough about your situation that I can tell you right now that a particular situation is far enough removed that you should consider it to either be *de minimus* or waived. I would suggest that we discuss it in further communication for future meetings.

MODLIN: Neal?

HALSEY: I would also ask that you re-examine the guideline that you mentioned earlier about having a line authority over individuals within the institution, university or otherwise, not being able to vote on issues of apparent conflict of interest. I think that guideline would preclude you from having most department chairs in universities. It would've precluded me as a division head supervising a number of other faculty from having voted on almost any vaccine issue during the years that I served on the ACIP because I supervised faculty who are doing research with most of the companies. I think it would've probably precluded Sam Katz, who served on this Committee for many years, from having voted on most issues. I'm not certain about that, but he's a department chair and was a department chair at the time. So I think that's something you don't really want—to not have the people who are a little more senior who have more years of experience working on this, especially if they don't control those monies directly, and they don't. I have no control over my faculty, I can assure you, and that they don't get any direct financial compensation, you know, from those grants.

MODLIN: Good point.

MALONE: That's an issue that I think we'll certainly consider. I would suggest that you write to us with your arguments about any of these particular points. That is, unfortunately, a gray area also. I can see arguments certainly going the other way, and yet I understand the point about it. One point that I want to hammer home here though is that we always allow discussion. That is a very significant waiver that we have provided. Even in the instances where we have very low numbers of people voting, presumably the minutes indicate a general approval by the other members. That should serve to further legitimate any kind of vote that's done by this Committee.

MODLIN: Fernando?

GUERRA: Kevin, in the incidence of holding of mutual funds, some of which are heavily invested in some of the companies that manufacture vaccines, are there any guidelines?

MALONE: A widely diversified portfolio is not considered an interest. If it was solely a vaccine sector mutual fund, it probably would be.

MODLIN: Tom?

VERNON: Two issues, Kevin. Having listened to the declarations of conflicts this morning, the rules as laid out will inevitably lead to a number of individuals on a number of votes not being able to vote, and in fact, calling upon the federal officials who are the *ex officios* to vote. Early in the Vaccines For Children Program, there was a great deal of sensitivity allegedly in Congress about non-elected officials; that is ACIP members voting on the expenditure of the federal budget. We would now be having votes on VFC in which it is federal officials who are voting on expenditures of the federal budget when it comes to the VFC votes. I think that is something to take into consideration; that is any political sensitivities that may remain there.

Second point, we've been very dependent upon our representatives on the Committee of government, state and local health departments being able to vote. I'm concerned about the interpretation of a state or local official as having a conflict of interest if his or her department has received a grant, small or otherwise, from a vaccine company. We often make those kinds of grants for purposes of educational programs or trying out innovative ways of delivering vaccines in the public sector. In the past, at least in one case, this has been interpreted as a reason for conflict of interest and inability to vote because a grant several years before had been provided to that local health department. So what is the—first of all, is there a twelve-month limitation on those and second, do those kind of grants create conflict of interests generally?

MALONE: I don't believe that we have ever stated that a state official had a conflict of interest based on a relationship. Certainly, we need to look into the extent of relationships and whether or not it's relevant. Currently, I don't think that we're excluding any state officials.

MODLIN: Thank you. I think the Committee has provided some reasonable feedback and counsel, Kevin. If there aren't any other burning issues here, I don't think we need to take any votes.

MALONE: By the way, I might mention that probably this afternoon we will be utilizing the *ex officios* to vote. It's unfortunate that the quorum is set at seven. It anticipated that we would have twelve members and of course we don't.

MODLIN: We'll have to count heads. Okay. Let's take a break. We'll be back at 11:15 to take up the rabies vaccine statement.

Could I ask everyone to take their seats please? While people are taking their seats, Gloria has just asked me to remind you that for those of you who are going to dinner tonight, that she needs to have your menu selections certainly as soon as possible and no later than the lunch break. Again, let me remind everyone to please speak directly into the microphones so that the conversation and discussion can be picked up by the transcriptionist. We don't quite have a quorum yet—one, two, three, four, five, six; yes, we do.

At each of the last several meetings, we've had some informational presentations led largely by Chuck Rupprecht. Since that time, a working group has been constituted to examine and rewrite the rabies statement. I can attest that that group has been extremely active in the four months since our last meeting and has made remarkable progress under Chuck Helms' leadership. Chuck will be leading off the discussion today. Thanks, Chuck.

HELMS: Thanks very much, John. Can you hear me? Okay. The working group on rabies immunization recommendations is bringing before you a draft document for your input today. It's essentially an update of the 1991 recommendations, which you may or may not have seen before. I presume most of you have. We hope that you'll be able to give us some good input here and that we can move fairly rapidly after this meeting to closure on this particular document. I'd like to just review the process that's gone on here initially. The working group was formed after the last meeting of the ACIP this past spring. Our charge was, of course, to update and revise earlier recommendations on rabies.

The working group included from the ACIP: David Fleming, Marie Griffin, myself and John Modlin; representing other groups: Carolyn Hardegree from the FDA and Robin Leffice from the FDA. We also had present a very helpful individual in Suzanne Jenkins of the National Association of State Public Health Veterinarians, and a large number of individuals from the Viral and Rickettsial Zoonoses Branch of the CDC, specifically alphabetically, Paul Arguin, James Childs, Kathleen Hanlon, John Krebs, Lisa Rotz, Chuck Rupprecht, Jean Smith and Tracy Treadwell. This group met by telephone conference three times between April and June. The draft that you have before you is a consensus document as of that last telephone conference call. There will be some minor changes to that, which will be introduced as Paul Arguin goes over the details of this document.

Over the past six months preceding designation of the working group, the CDC staff had prepared a preliminary update of the 1991 ACIP document in consultation with the Counsel of State and Territorial Epidemiologists and the National Association of State Public Health Veterinarians. The staff's update incorporated ACIP discussions and decisions related to rabies over the previous two years. The minutes were gone over and essentially critical elements related to rabies included in the document. The working group has reviewed and modified this preliminary staff update. There is basically consensus around the document that you have before you. It isn't uniform consensus. In specific, the wording of the section on bat exposure that you have before you was not entirely perfect as far as certain individuals in the group were concerned, but subsequently, we've been able to work on that and Paul Arguin will present a resolution of that difficulty.

Secondly, there was a considerable discussion in the committee about whether an evidence-based format for this document would enhance the usefulness of it. Our plan for this hour is to ask, first, Paul Arguin to review the major changes between this and the previous draft for you. We'd like to get input from the ACIP on this draft bat exposure statement that has undergone some modification, and also, to get some input from those folks here about whether an evidence-based format would enhance usefulness of this document or not. The remainder of the time, after we sort of focus on those two particular areas which are important to the working group, will be open to discussion of issues that you bring to the floor.

Also I would like to say at this point that if at the close of this session we haven't had time to hear everybody's point of view, what I would advise everyone who has not been heard to do is to write down on your draft your comments, your changes that you'd like to be seen and please deliver them either to me or to Paul at some time during this meeting so

that the committee can work with them afterwards. Some of the vaccine companies have already done that and have given us some materials to look at. I'll now turn the podium over to Paul, who'll go over the document itself. Are there any questions or concerns that I can answer?

ARGUIN: Good morning. The rabies prevention guidelines were last comprehensively updated in early 1991. At that time the document was being prepared, the total number of animal rabies cases reported annually had been decreasing, and there was on average only one human rabies case per year. The majority of those cases of human rabies were attributable to exposure to dogs outside the United States. Since then, the number of reported animal rabies cases has almost doubled, peaking in 1993. Human rabies cases have also increased in number with the majority of these cases caused by variants of the rabies virus associated with domestic insectivorous bats. In addition to the changes in rabies epidemiology, new rabies biologics and new recommendations for the administration of the biologics are in use. The time seemed right for another comprehensive update of the rabies prevention guidelines.

The purpose of this document is to provide primary health care practitioners and public health officials with simple, straightforward guidelines about both pre-exposure and post-exposure management of persons who are at risk for infection with the rabies virus. For users of the document familiar with the 1991 version, the overall structure of the document has remained the same, but most sections have been updated. We can now review the updates in the section. I hope everyone has a copy.

First of all, just glancing at the table of contents, you'll notice that the pre-exposure section has been moved before the post-exposure section. It just seemed like a logical progression. On page 1, you'll notice there are italicized comments underneath the title. These now include a brief mention of some of the major changes in this document, including the recommendations about bats, ferrets, the new rabies vaccine in use and the administration of human rabies immune globulin. Pages 2 and 3 introduce that most recently FDA-approved rabies vaccine, which is produced by Chiron Corporation and marketed in the U.S. under the name of Rabavert. It's a purified chick embryo cell vaccine and referred to by the acronym PCEC.

On page 3, line 24, the definition of foreign travelers for whom pre-exposure prophylaxis is recommended has been made a little more precise. Previously, it had been recommended for travelers who stayed abroad for more than thirty days in enzootic countries. The time period was intended to distinguish these high-risk persons from regular tourists. The current wording, as you can see, starting on line 24 spells

out the risk factors a little more precisely. On page 4 in table 3, in addition to moving foreign travelers from the frequent to the infrequent category, the recommendations for serologic testing with boosters if needed—you see in the last column of that table—was made consistent for both the continuous and frequent categories.

There were no major changes on page 5. Page 6, however, the first small change, you'll note that in table 4, ferrets are now included with dogs and cats to be treated as domestic animals. Further down the page, starting at line 20 is the section on bats. Due to the changing patterns in human rabies cases and the emergence of bat-associated variants of the rabies virus being implicated in the majority, in October 1997, the ACIP adopted specific language recommending post-exposure prophylaxis for persons who either were or likely were bitten by a bat. Since that time, concern has been raised that the recommendations were not being uniformly interpreted and applied around the country resulting in increased numbers of inappropriate administrations of post-exposure prophylaxis.

As of the last working group meeting, there was still some disagreement about the precise wording to clarify the intent of the section. Since then, an additional sentence has been added and approved by most of the working group members. Okay. So this is the entire section. The new sentence is highlighted right here; I'll read it for you. It reads "Based on the available but sometimes conflicting information from the 21 bat-associated rabies cases since 1980, a bite was reported in one to two cases, apparent contact without a recognized bite occurred in 10 to 12 cases, and no history of exposure to bats was elicited in the remaining 7 to 10 cases. However, an undetected or unreported bat bite remains the most plausible explanation for transmission." It's expected that this combined with the final sentence that you have in your copy in that section will clarify the intent of this recommendation and reduce the number of persons getting post-exposure prophylaxis after simply having, for example, a bat fly through their house.

Page 7 does not contain any substantial changes. Page 8, table 5—the new recommendation previously approved by the ACIP to administer the full dose of human rabies immune globulin at the bite site, if anatomically feasible, has been inserted into the table as well as the text. On page 9, table 6, this is a new table that was added, which lists cell culture vaccines widely available outside the United States, which U.S. citizens traveling abroad may be given if they are exposed and started on a post-exposure regimen before returning to the U.S. In the old 1991 version, there was a section entitled *Unintentional Inoculation With Modified Live Virus Vaccines*. This section has been removed since these vaccines are no longer available. In addition, statistics and references have been updated throughout the document. Other than

that, this concludes the review of the major changes that have occurred in the updated guidelines.

HELMS: I trust that was fast enough for everybody. I'm sure a lot of this has flown by. Good. Thank you, Paul. I'd like to, while this particular document is up on the screen, get some feedback from the group about this. To give you a little background here, the uneasiness that was within the working group about the wording of this section was not about the conclusion—which was that under certain circumstances it may be appropriate to immunize a person who may have been potentially exposed to disease or bitten—but was really the inclusion of data to support that conclusion and what data there was in the document itself. This was, if you will, the compromise that was worked out over the last few days and transmitted by e-mail amongst the group. The individuals, all but John Modlin, that we've been able to poll have generally accepted this idea. I certainly would open it up to the rest of the ACIP and other individuals to comment on.

MODLIN: Fernando?

HELMS: Fernando.

GUERRA: Chuck, I guess relevant to this particular section, what is the specificity of the current brain analyses with, you know, special stains that are used for trying to diagnose rabies in a bat given the fact that one is dealing with a very small surface area, specimens that are taken and processed and what have you?

HELMS: You're talking about specificity now?

GUERRA: That's right.

HELMS: I'd have to ask Paul that.

ARGUIN: I hope that there is someone here from the rabies laboratory who could probably speak more precisely, but using both fluorescent antibody techniques as well as PCR, it is quite specific, both to—I can't assign a number—but I think it's very, very specific as well as sensitive to both make the diagnosis of rabies in the bat as well as to type the strains of rabies virus to determine if there's a bat-associated variant or one of the other reservoirs. The same would apply for once the diagnosis is made in the human, to go back and type that variant to determine which reservoir it's associated with.

GUERRA: This is well validated across laboratories around the country and/or the world where the specimens are processed. I have great confidence in our laboratory within our department.

ARGUIN: Correct. Monoclonal antibody techniques are used by many laboratories. Fewer laboratories sequence by PCR. Like I said, if someone from one of the rabies laboratories would like to comment on or to assign a number to how specific and how good the reference laboratories around the country and around the world do it, I'd welcome that comment.

SMITH: I'd be happy to comment. It's an excellent task.

MODLIN: Could you use the microphone please, and identify yourself please?

SMITH: I'm Jean Smith from the Rabies Section at CDC in Atlanta. We and all of the state laboratories participate in proficiency tests of the rabies diagnostic procedure. It's excellent; it's been in place since the 1950s. We have no complaints about sensitivity or specificity.

MODLIN: Chuck, go ahead. Why don't you go ahead? Well, there were some other comments.

HELMS: I think Dr. Plotkin over there was. . .

PLOTKIN: This is a relatively small point, but concerning people who need repeated boosters, we just published a paper suggesting that one could differentiate long-term—rather people who respond well and may not need boosters on a regular basis from those who do need boosters by their response to the dose at a year: those above thirty units having long-term persistence and those under, not having long-term persistence. So it may be of some help to people who for reasons of exposure need repeated boosters.

LE: Yes. Actually, I was going to ask that question, which I thought your paper actually was very helpful for people like us in the clinic. Kind of looking at the CDC recommendation as well as this new paper, I think it was published in March or April of the *JID* issue. I have it here—actually, May of the *Journal of Infectious Diseases*. If we were to go on to evidence-based criteria for this recommendation, I wonder on table 3 in terms of a booster—you'll check the titre and booster and so on—are those based on data or just kind of an arbitrary risk assessment? This paper seemed to really show the logic behind the testing; however, there's one difference. It's that that schedule called for testing the titre about two weeks after a booster given at a year post, which is not the routine schedule recommendation. So I don't think I'm asking to change the whole document this late, but perhaps inserting that reference for clinicians to look at would be very helpful.

HELMS: Okay. I wonder just for a few minutes, I'd like to focus on this to make sure that people are comfortable with this, and then move on to the

evidence-based data for maybe five minutes, and then jump into all the other aspects of it. Alright, Bill.

SCHAFFNER: After a poll of this, I'd like to speak in favor of including the highlighted sentence. I think that that's very, very useful information. In fact, I think it's so useful, that you might consider breaking up that long paragraph so that it becomes more prominent and you don't have to search for it. As Chuck and I were speaking in the break, let me add something for the consideration of the Committee. I'd like to direct your attention to the "remaining seven or ten cases." Those are the cases where there's no history of exposure to a bat. My comment comes from a recent experience with just such a case.
This was a woman who came to our institution from a rural area, was discovered in due course rabies with the silver-haired bat-associated strain. At the time she was being cared for, there was no known association with a bat. In fact, there still isn't despite extensive investigation. Now I'd like you to put yourself in the mind set of her neighbors. Her neighbors also had no association with a bat. Obviously, this was inquired of a lot. They lived in exactly the same environment she did. So their logic, and I think you can appreciate it is, "We're just like her. Why don't you give us the vaccine? It makes sense." The argument that I found most telling was that absent the circumstance where a known rabid animal bites a series of people, absent that circumstance, rabies does not cluster. We have single cases. If there is information to the contrary, please correct me. I think it's—I would propose that there be a paragraph that addresses that issue. This obviously is in the context of attempting to guide the use of vaccine to those who are genuinely at risk, not just to those who are fearful.

ARGUIN: I guess in the table where people are categorized into continuous, frequent, infrequent and no increase above the general public, the general public also does not have any knowledge of being exposed to a bat last night as well. So therefore, their risk is not greater than to the neighbors who also were not aware of being exposed to a bat.

SCHAFFNER: I don't want to prolong this.

ARGUIN: Yeah.

SCHAFFNER: That's technically correct, but it's not persuasive. I'm just trying to suggest that we add a paragraph that in the context of these cryptic cases, they occur singularly; the general community is not at increased risk; see the table if you like; there's no need to give vaccine to the neighbor. . .

ARGUIN: Also with these cryptic cases. . .

SCHAFFNER: . . .if there's agreement to that.

ARGUIN: Sure. Yeah. Also with these cryptic cases, it's not necessarily that they have been exhaustively investigated that all data available is known and we know that no bat indeed was there. Some of these cases, many of these cases, the person has died and there's no way to obtain that history.

SCHAFFNER: Exactly.

ARGUIN: Yeah.

HELMS: Rich?

CLOVER: I really would support the last comment. The problem with this is is this is a numerator. We have no idea what the denominator is. When you just read that statement, you think it's a high probability that you won't know where the exposure is. People forget that the denominator —the number of people who are exposed to bats, does anyone know that number?

ARGUIN: Huge.

CLOVER: Yeah.

HELMS: Any other comments about this issue?

MODLIN: Just a quick question that perhaps Stan Plotkin and there may be others in the room who might address, and that is the issue of communicability of the bat rabies variant, and whether or not there are any new data that would suggest that the possibility of this being more highly communicable than other rabies variants. That issue has been brought up. Obviously, I believe it was Hiller Koprowski that postulated that based on the ability of the virus to grow in fiberglass. Stan, do you have any new information on that? Does anybody else? He's shaking his head no. Fine, we'll move on.

HELMS: Dave:

FLEMING: First off, I just wanted to compliment Paul in particular for working on this section so diligently and trying to listen to so much input. I think one of the points that you made in response to Dr. Schaffner's comment is important, and that is the issue that for many of that latter category of cases, it's not that we know that there was not a bat exposure, but rather that we don't know because information sufficient to obtain definitiveness just wasn't available. I'm curious to know because those of us on the working group have been so close to this,

whether that concept in your minds comes across from that statement because in my mind, that's a fairly important point for people to understand. So do people feel, who have not been sort of word smithing this past couple of weeks, that that point is made here or does that need to be more explicit?

HELMS: Rich, are you saying, "Yes, it needs to be made more explicit"?

CLOVER: Yeah.

SCHAFFNER: Yeah, I would agree.

HELMS: One more, Bill?

SCHAFFNER: Yeah. You knew I had another. I wonder if I could direct your attention—and it flows from David's comment too—to page 5, right at the bottom. It's in this context, the paragraph that begins on line 52, "Apart from corneal transplants, bite and non-bite exposures inflicted by infected humans could theoretically transmit rabies"—and then you get to the punchline of the sentence after that long lead-in— "but no laboratory-diagnosed cases occurring under such situations have been documented." We're really talking about human-to-human transmission here. This is terribly important. This is Coles to Newcastle as you know. In your providing information to people who are caring for a patient with cryptic encephalitis who then is discovered to have rabies, all the health care workers, who should appropriately have been immunized? Also, not an easy circumstance.

I think, once again, the single most important epidemiologic concept is that person-to-person transmission has not been documented. So I would offer as a suggestion a separate paragraph with a bold heading—**The Lack Of Person-to-Person Transmission**—and then to start that paragraph with a strong declarative sentence, not one with all these subordinate weakening clauses to enter. Say, "person-to-person transmission has never been documented either in the community, or in the setting of the hospital or health care situation," something like that because it was that, once again, that epidemiologic quantum that was very persuasive in our being able to manage our own case very, very well. We had over 200 people who had some association with this patient—three shifts, et cetera. Four took the vaccine. The hospital that sent the patient to us, virtually everyone who had contact with the patient was immunized.

HELMS: Thanks. Another good point, Bill. Yes, Fernando.

GUERRA: On page 1, I wonder if it might be helpful to include in about that middle section where "twelve (33%) of the 36 human rabies deaths reported to

the CDC from 1980 through 1997 appear to have been related to rabid animals outside the United States," if there is some indication of where they came from, the countries of origins, et cetera because I think that if in fact—and perhaps to the point that Bill Schaffner was making—that there are those cases of cryptic meningeal encephalitis that sometimes are not recognized as being rabies when they show up in emergency rooms or end up in the intensive care units in certain regions of the country. If one knows the country of origin, one could move as the cause of the cryptic meningeal encephalitis rabies higher up on the list than one otherwise would've thought of doing. I just wonder if you have any indication of where some of the countries of origin might be? My sense is that a number of those came from Mexico or Central America.

HELMS: I've seen Iran and Mexico. What else?

ARGUIN: Nepal, Phillippines, Thailand, Bangladesh, I believe; however, we may not want to put too much detail into the document. I would like to try and keep it streamlined with the recommendations. Certainly, I think if we were to highlight the countries where it has occurred—and certainly there's other countries as well that have enzootic dog rabies with large amounts of uncontrolled stray dog populations—that if it hasn't occurred yet, it wouldn't necessarily get highlighted. People are always encouraged to contact state, local as well as the federal authorities for additional advice in managing some of these cases where someone says what's the probability of someone coming from who knows where—any foreign country—what's the frequency of rabies in their stray dog populations? So I'd consider that as well.

HELMS: Some comments on evidence-based format might be good to bring in here.

MODLIN: I think Pierce had another.

HELMS: Pierce?

GARDNER: The document certainly has much more about serologic testing, I think, than previously. That's become sort of part of the strategy. The last time I went through this, serologic testing was not widely available to a lot of people. Has that been improved? Do all states offer serologic testing, neutralizing antibody tests now? How hard is it for the practicing physician to get blood to a place where it's going to be answered in a reasonable time?

ARGUIN: There are commercially available places in the country. I think they have pretty good turnaround times as well to get the serologic testing. I don't think it's available in every state, but they know where it needs to be shipped to.

GARDNER: Is it costly? It's a neutralizing test. Is it a costly serologic test? Do we know?

ARGUIN: I don't know.

GARDNER: Does anybody know what the cost of this is?

ARGUIN: It's less expensive than a booster dose of the vaccine.

HELMS: Okay. Comments on evidence-based format, please? This is an issue with regards—do you want to answer that? Go ahead.

SMITH: I just want to comment, yeah, about the serologic tests. Yes, it is cheaper than a dose of vaccine and certainly would be advisable, especially for people who have long-term employment in rabies laboratories. Rather than having booster doses every six months to every year or two years, to have serology done. I think the prices—a number of the state laboratories will actually perform the test in-house and CDC does offer training for those state laboratories who wish to offer that service to their employees. This certainly would be cost-effective for them. It is commercially available; the cost varies. It's about $25 for a serology. It gets to be more expensive because of the shipping—the cost of shipping serum back and forth across the United States—but on average, we say about $30.

HELMS: Those of you who've had a chance to review the document on rotavirus and to look at the table that they have set up in there for evidence-based—the evidence that the recommendations are based on —will have an idea of the issue that arose within our working group on rabies with respect to including a table like that in this particular document. The pros in terms of arguments that arose for it are one, that it's clear that this is the trend and this is the way things are moving in terms of recommendations cited for all different sorts of medical treatments, whatever. So it would be appropriate for a document like this maybe to be consistent.

Secondly, it's helpful in showing too where research might be needed in showing up data deficits in terms of making recommendations. There are some cons, however, that came to the floor in our discussions. A couple of them I was able to recall, include when you're dealing with a vaccine, if you will, as old as the rabies vaccine is where so much of the understanding of its efficacy and value is based on experience, if one really laid out, for example, the evidence basis of it, what would it look like? Would it be necessarily very impressive or not? There certainly have been no randomly controlled placebo trials of this particular agent. One would wonder with this particular type of update on an old vaccine, is such an evidence-based format useful and would it help?

Secondly, there was some concern expressed that individuals in reading such an evidence-based table, seeing that the data, for example, was insufficient, or classification C or whatever you want to call it, were seeing that the level of evidence may be, you know, opinions of authorities or something that is presumed to be less helpful that individuals actually might make decisions based on a table like this. I think that is a legitimate concern in regards to this.

Thirdly, it does add another table to this document. It adds some more information that has to be laid out. As a group, I think we had consensus that it probably wasn't necessary to have such a table, but there was some strong concern expressed that indeed, perhaps we ought to. I'd like to hear this discussion. It goes beyond, in a way, rabies. It will go to updates of many other vaccines here. Any thoughts?

FLEMING: Well, my primary concern actually does extend well beyond the rabies statement. I think it would be useful at some point—perhaps at the next meeting; I don't know—to have a more explicit discussion around, for the purposes of ACIP recommendations, what criteria we're going to be using for grading recommendations. I think an explicit concern that I have is that many of the key policy recommendations that are contained in ACIP, by their nature are not amenable to a randomized clinical control trial. To give the answer to this issue around bats would be a perfect example. It is not ever going to be possible to randomly give people either post-exposure prophylaxis or not in this setting.

There are many other examples. Even the recommendation for universal use of a vaccine—for example, rotavirus—is not dependent solely on a randomized trial showing safety and efficacy. My fear is that by holding up that randomized trial in our tables as being the gold standard, that we in essence may be self-defeating; that we are establishing a standard for most of our recommendations. That is not feasible given the nature of what it is that we're recommending. That was a concern that I had with trying to create such a table for the rabies statement.

SNIDER: I just wanted to comment, you know, from the agency perspective. It's clearly our intent to try to move to evidence tables and quantitative approaches to the extent that it's possible. It's not that it's just the fad. It's the fact that in order for now and in the future for people to adopt recommendations, a variety of individuals, but more importantly professional societies are demanding that certain types of evidence be presented before they are going to change the behavior of their organizations, change their financing mechanisms and so forth. So you know, having said that, I mean I want to hold that up as the ideal.

At the same time, I think we all recognize that in the case of rabies vaccine, we could be talking about anthrax; we could talk about a lot of different situations in which we're not going to be able to produce certain kinds of information. I think that we have to be very pragmatic about this, and cite evidence and utilize evidence where it's available. At other times, it won't be available, but there will be compelling arguments to be made, such as the long use of this and the lack of or the paucity of failures among those who've been exposed and not developed rabies and so forth. I think most—the average person as well as the average practitioner will regard as compelling evidence, if you will, even though it doesn't fall under these classifications.

I think one of the other functions, at least of going through the exercise that we want to be sure we don't miss, is the opportunity to identify research that could be done to address certain questions we might have. It may not be around the efficacy of the rabies vaccine, -- but there may other issues—not necessarily with this vaccine—but with others, such as interactions and so forth where we want research to be done. So going through the exercise itself, whether we put a table in or not, I think has some utility. So I would not want to—I feel it would be remiss for me not to say that we should go through the exercise of seeing what it looks like, and what the implications of the evidence table are for gathering appropriate evidence that could be gathered to help support some of our recommendations.

HELMS: Anybody else want to discuss this point? Marie.

GRIFFIN: I guess I was the one on the subcommittee that was pushing for the evidence table. The program does have problems because we have two recent statements that use different criteria—I think the combination vaccines and the rotavirus. I think it would help the program, if they're going to be expected to do evidence tables, to try to adopt some kind of uniform classification system. So maybe we should do that as a Committee. I think if we're only going to do this for new statements, I guess my feeling was we need to do this when we revise the statement, and that it helps point out the strengths and the weaknesses of the statement.

I think the rabies though, in talking to the program people, I mean, there are clinical trials in non-human primates that I think are referenced, but even those of us working on the statement don't know about them. I think in a lot of instances, there's more information that program people know about that's just not general knowledge. I think the evidence table might actually be a way to muster the support for the recommendation.

HELMS: Fernando.

GUERRA: I certainly agree with everything that has been said. It seems to me that given some of the work of the Community Preventive Services—guidelines development by that task force—that is really moving in the direction of trying to generate as much evidence-based to support a lot of the recommendations, and certainly within that, the area of vaccine preventable diseases is one of those sections that is being looking at. There is already some effort going on to try to generate, you know, the different areas where evidence-based exists.

I think the other reason why we need to do it—and I agree with David that there are those areas where probably we'd get bogged down because it's just not there—but that one could certainly make reference to that and try to assemble what will help to bring some strength to the recommendations. I think that in the instance of managed care and reimbursement systems that are in place and/or emerging, they're asking for more and more of that before they're willing to pay for services, or for interventions, or vaccines or medications. So I think it's incumbent on us. Maybe we could have it as an item for discussion at the time of the next meeting.

LE: Just for my own education, back to my original question about table 3 and page 10—the recommendation for serologic testing. Are they based on expert opinion, tradition type of thing or whether there are studies for this, you know? I just want to know.

ARGUIN: A specific titre has not been shown to be protective per se. Rather, a level has been determined to be reliably detectable. It's used as a surrogate for immunity; it does not prove immunity.

LE: So the guideline is a little bit arbitrary? Is that right? I mean, in terms of also the risk categories—continuous, frequent—versus three-month, two-year testing is kind of an expert opinion, arbitrary type of guideline?

ARGUIN: Correct. Yeah. For the continuous, of course, it's a little tighter to ensure that these people are protected.

LE: I think it may be useful then, on page 10, line 35, before saying "the following guidelines are recommended," perhaps qualifying by saying "expert opinion" or say that's something you can do, but you know, those guidelines come from somewhere and perhaps saying just those are expert opinion type of guidelines rather than an outcome study or something.

MODLIN: Chuck?

HELMS: Yes.

MODLIN: Get the comments of both Stan and then have Dr. Ganiats.

PLOTKIN: I've always wondered in this day of science why there isn't a fourth category, and that is evidence based on animal studies. Now rabies and anthrax, for that matter, present perfect examples of that where the animal systems are pretty good. Obviously, there are diseases for which the animal systems are terrible, but in these cases, there are good data on a number of these points based on animals. Now obviously, we'd prefer to have human clinical trials, but we can't. Nevertheless, if you have a fourth category, you could stipulate which recommendations are based on solid animal data.

SNIDER: I think that's an excellent point, Stan. I think as Dave was alluding to earlier and Fernando, I think we can develop some criteria. We need to develop our set of criteria for vaccines. Clearly, one of the, you know, sets of criteria that could be utilized are animal study criteria, which of course, the U.S. Preventive Services Task Force is a generic set of criteria they had and didn't find necessarily appropriate for most of the interventions they were talking about. In the vaccine area, it seems to be one of the critical criteria that one might add to the repertoire.

HELMS: You know, to bring this issue a little bit to closure around this vaccine. . .

MODLIN: One more comment back here, Chuck. Okay. I'm sorry.

HELMS: . . .just around evidence-based, it sounds like the exercise is probably a good thing to carry out here. I'm not so sure the data will be useful to the practitioner in the field. Perhaps it would be a good idea for the staff to develop a table based—just to take a look at it and for us as a working group to sort of decide whether that's going to be useful to have for people and not, and in particular, to take Dr. Plotkin's idea here of trying to put together the animal data with this. It may make it look a lot better than it otherwise might. Sorry to interrupt.

GANIATS: No problem. I'm Ted Ganiats, American Academy of Family Physicians. In general, we're an organization that likes the idea of evidence-based medicine. I think it's important to remember a couple of things. First of all, you don't have randomized trials to say that cigarette smoking is harmful. So there is a precedent to act on things that are less than a randomized trial. On the other hand, we also have very little evidence on the effect of evidence-based medicine. You have very little evidence on what are the policy and clinical implications of having an evidence table that doesn't include the animal models or in any other way minimizes the efficacy of the rabies vaccine. I think that if as a policy it would reduce the use of rabies vaccine by 20 percent,

would anybody accept that? That's a plausible concern. I would suggest that strong consideration be given to careful evaluation of the use of an evidence table in a disease like this when we don't really understand how the evidence table is going to be used in reality.

MODLIN: Okay. We do need to bring this to closure as Chuck suggested. It sounds to me like—let me ask you would the working group prefer to go back and develop an evidence-based table, and take a look at it and bring it back to us or would you like some more direction? Is this something that we should take a Committee vote on that would be of value?

HELMS: I don't think the Committee needs to vote on it. I think going through the exercise is important. Depending upon how you feel, frankly, whether you leave it up to us to decide whether to put such an evidence table in or not, I think we can make that decision or bring such a decision back to you.

MODLIN: Originally, we'd made such good progress with this statement that we thought that we might be able to actually take a vote on the statement, but it sounds like to me like there have been several suggested changes. I suspect most members of the Committee would at least like to see the language for changes that have been suggested by Bill Schaffner and others, and probably almost certainly would like to see the nature of the evidence-based table. So my suggestion would be to send this back to the working group and to staff. For members, for everyone who wishes to make comments on the draft, to please get them in within the next three to four weeks. Hopefully, we will put this on the agenda for the October meeting and make a final decision on the rabies statement at that time. Does anybody—Fernando?

GUERRA: Two points—one, I think that it should certainly go back to the committee and they can work on that. It would be very helpful, it seems to me, so that we can have our own working consensus as a Committee about how we're going to use evidence-based with the parameters of that and the guidelines that we will follow because I think that, you know, it is sort of an evolving science and it would be very helpful. I just wonder, John and Dixie, if that might be something—I'm sure there must be staff at the CDC that could perhaps give us a perimeter on evidence-based use and the development of that, the tables, et cetera.

MODLIN: I suspect it's going to be something we're going to have to consider on an issue-by-issue basis because it was. . .

SNIDER: Well, it may be and I think the generic, you know, discussion, you know, can be interesting. It seems to me, based on some points that have

been raised here, that there are some very legitimate things to put in "an evidence table" that maybe haven't been put into an evidence-based table before and yet perhaps should be. One Stan mentioned, which is, you know, if there are suitable animal models, you know. Is there evidence of protection? Another that's been suggested is there—has there been proof in practice, you know, of 10, 25, 50 years, whatever, you know, that an intervention appears to be working?

So I think one of the critical things that someone who is involved in prevention effectiveness or any of the evidence-based activities at CDC is not going to be able to answer is, what are the criteria that you want on your list? Once you tell them the criteria you want on the list, you know, then they can tell you how you can use those things. Again, I think, you know, I'm pretty happy with some of the evidence tables that people have come up with in this recent round. We don't have a long experience in putting together evidence tables. I think we're moving in the right direction, but as John says, you know, it may be that the things that—certainly, the problem we're going to have is that the things you pull out of the document to make a statement about whether there's evidence or not is going to vary from vaccine to vaccine because we're going to make some statements, for example, about whether you can have co-administration with another set of vaccines where you'll want to make a statement about whether you have data or not.

So from that standpoint, I think there's going to be two sets of criteria: one that are kind of standard across all vaccines—we could probably come up with that—but then there's going to be another set that we're going to be having to pull out of each set of recommendations to alert us all to the fact that in some cases, we don't have anything but an expert opinion to support it, which is a signal that it ought to be, perhaps it ought to be considered for inclusion in a research agenda.

MODLIN: It sounds to me like the Committee certainly wants to, at the very least, consider an evidence-based table. Rick, you had your hand up?

ZIMMERMAN: Just a couple of comments on that. I speak in favor of the idea of the evidence-based table. Obviously, I've done that previously, but there's a couple of things. One, somebody else may make one and they may not have the expertise that sits either at the CDC or at ACIP or have gone through that process. So they may make one with less broad exposure. I think this is the perfect situation with a history of rabies; that if someone just goes and looks at randomized control trials from a MedLine search, they're going to have less evidence. So actually, you might do better service to provide one so that someone else doesn't come up with one that doesn't have the breadth that you're looking at. It may well need to be individualized. So I would speak in that light in favor of it.

I also think that we should recognize that we have in this and other documents words like "consider." I don't really know what "consider" means. I mean, "consider yes, you should probably do it;" "consider maybe you should do it?" I don't know what that word means. I suspect if we were to have an anthropologist go and ask each one of us in this room, we would probably have about thirty different answers. I think that the evidence table could give a little better structure about what you mean to words like "consider" and "recommend."

GUERRA: John, just one more for clarification. In the document, I did not see any reference to infants. You refer to children and adults, but has the vaccine been used safely in infants and should we mention that because it's a question that does comes up?

ARGUIN: No age restriction has been on the post-exposure prophylaxis. So if the infant has been bitten by the bat, it would be recommended that the infant receive it as well.

MODLIN: Mimi?

GLODE: Again, if we're just in the general categories, I'll write this down for you. I expected to be more educated about ferrets after I read this than I was when I finished reading it. So I wanted you to tell me whether there were cases transmitted from ferrets to humans, what the prevalence of rabid ferrets was and do they need to be immunized every year? I didn't—you know, I wanted to read that, but I didn't. I saw it in the table of contents, but there really weren't very many facts about ferrets and rabies.

MODLIN: We had a presentation on ferrets and rabies about two meetings ago, as I recall, that Chuck presented, but it's not in the—good point—it's not in the. . .

ARGUIN: I would refer you to U.S. surveillance data regarding the specific numbers of ferrets. The ferret recommendations were included after the National Association of State Public Health Veterinarians adopted that based on data which is now in on the pathogenesis of rabies in ferrets. So I guess the 1998 compendium as well as the surveillance reports, I guess would be good places to look for that.

MODLIN: Okay. Georges?

PETER: One practical comment is inevitably these situations arise in a weekend and the availability of experts is limited. The statement often says "consult public health officials," which is very appropriate. I think we need to find ways to make the document more user-friendly. One is when you consult public health officials, they're basically using the

information on pages 7 and 8 or 6 and 7. I think also the footnote that's in the very front of the table which says "if you can't reach the public health official to call CDC" could be indeed added as a footnote to the table in order to expedite communication because there's always a lot of anxiety about people who think they have the answer, but they're not entirely sure. It's such a devastating disease.

So I would indeed make sure that "consult public officials" is sufficient and people understand how the public health officials are making their decision. I think that's simply a question of organization. The other point is on page 8 where it says that "administration should begin immediately." That creates a concept that you need to start five minutes from now. I remember past recommendations have been "ideally within 24 hours, but as soon as possible." I think the addition at least of that type of phraseology would give people a time of reference in which they needed to make contact with the appropriate infectious disease expert and public health officials.

ARGUIN: Thank you. Yeah. I believe—I can't find, I don't know where it is right now, but the language is in there to emphasize that it's considered an "urgency" not an "emergency." So even though the word "immediately" or "as soon as possible" is in there, there's always time to consult state, you know, local. . .

PETER: Right.

ARGUIN: . . .federal public health.

PETER: Well, you see, it's the fact like most documents, unfortunately, people don't read and remember every single sentence. So it's the word "immediately" that I think needs to be at least rethought. Then I think the following statement about the fact that even if it's, you know, discovered seven days later, twelve days later, you can get post-exposure prophylaxis is very helpful in terms of the outside limit in which you would still give post-exposure prophylaxis.

MODLIN: Good point. Thank you. I'd certainly like to thank Dr. Helms, Dr. Arguin and Dr. Rupprecht, who I don't see here today, all of whom— and the working group—all of whom have worked extraordinarily hard on this over the last few months. It sounds like there's a little bit of work left to do, but most of it has been accomplished and accomplished extraordinarily well. We will revisit the rabies document just very briefly, hopefully in October for a final approval. It's lunchtime; let's reconvene at 1:15 sharp. Thank you.

SNIDER: Barbara's here. When we reconvene, let me go ahead and present these things.

MODLIN: Fine.

SNIDER: Would everyone take their seats please? Could everyone please take their seats and quickly terminate your conversations? Please take your seats; please take your seats; please take your seats. Do I sound like a broken record? Thank you very much. What I'd like to do before we get started is to recognize the two people I mentioned earlier today—one of whom who was not here and so I did not make this presentation. To both Barbara DeBuono and Marie Griffin, I want to present on behalf of CDC our thanks. That comes in the form of a letter from our Director and a certificate, as well as a book—the history of CDC—otherwise known as *Sentinel of Health*, written by Elizabeth Etheridge, which is we think a pretty good book, and also one for Marie for traveling back and forth to California.

MODLIN: I have a couple of just very quick housekeeping announcements. I understand that there's still one or two members that haven't turned in their signed waivers. Also, this is the last chance for anyone who wants to join the dinner party this evening to get your reservation requests and any requests into either Gloria or Kathleen. Okay. It's time to discuss the rotavirus statement. The reason why we scheduled this for after lunchtime was to give me an opportunity to don my suit of armor here. We do have two hours dedicated to the rotavirus presentation. The statement was discussed in February and as everyone will remember, there were one or two key votes that were taken by the Committee in order to provide some direction for the working group and for the subsequent preparation of the statement.

The statement has been revised on the basis of Committee feedback and also been revised again after deliberations of the working group conference call about a month and a half ago. In the process, we've identified several issues and some areas where Committee members felt that—asked us to reconsider or consider some of the issues, or revisit some of the issues. We also have some new and updated data as well. So we're going to address these in a series of very brief focused presentations that are listed here. Hopefully, each one will be five minutes or less. What I'd like to do would be to provide some opportunity for important questions and discussion at the end of each of these presentations.

I'm going to take the liberty of limiting questions and discussions to Committee members, and liaisons and *ex officio* members for at least the first portion of the discussion in order to get through this. Then at the end, we'll open up the floor for a full discussion. We'll begin with an update on cost benefit analysis by Roger Glass. Roger is going to update us not only on the new cost benefit data, but on some new surveillance data and on the serotype—some new information on

serotype Lyme disease. We'll continue on with some information on risk group analyses that Joe Bresee has put together based on some data from Washington State and also from the Indian Health Service.

We've asked Peggy Rennels to come back and discuss some new information or at least a newly published study—not necessarily new information—on adverse events and to put particularly the febrile reactions that occur following rotavirus immunization into some perspective. I'm going to spend just a minute or two on rotavirus infection in immunodeficient patients. Then we have some new information on provider acceptance that has just very recently been obtained. I'll share the floor with Jeanne Santoli from the National Immunization Program. Then I'll wind up reviewing some of the policy issues that several members of the Committee felt that we needed to address at the last meeting. So we'll start out with Dr. Roger Glass.

GLASS: Thanks very much, John. I'm delighted to be here. Someone told me this was round fifteen of the fight, so I'm happy to be back again. It's almost three years since we first began introducing you to the subject of rotavirus vaccines. Just to focus on what we're dealing with, I've put up a summary of the disease burden of rotavirus in the United States to remind you that this is a disease that every child gets or an infection that every child gets in their first few years of life. So we estimate somewhere around 2½ to 3 million cases a year—lots of clinic visits, about 1 in 10 children, 1 in 9 children; lots of ER visits, about 1 in 24 children; hospitalizations around 50,000 a year; and a few deaths and significant cost.

The impact of this vaccine then as we thought about the impact of the vaccine in our surveillance, the best surveillance that we're dealing with on the most costly outcome, medical outcome or hospitalizations. When we look now, about 160,000 to 170,000 hospitalizations for childhood diarrhea a year, about 10 to 12 percent of all hospitalizations of children under five, you can see this winter seasonal peak occurring primarily in children six months to two or three years of age, which we believe is primarily due to rotavirus. We have substantial evidence to that effect. The impact of the vaccine would be to flatten out those curves. So that's the hope and the aspiration of this vaccine program.

Of course, there are about 2,000 children a day who die in developing countries and the longer term prospects of this vaccine. The real impact will be in developing countries. Today, I want to start on my little brief presentation with Andy Tucker, who did the cost effectiveness analysis. Andy was an M.P.H. student. You've all received the cost effectiveness analysis, which was published in *JAMA*. At the last meeting of ACIP, we were asked to update this with new information about adverse events, particularly hospitalizations which were the most

costly outcome. So Andy has done that repeat analysis. Andy, thank you.

TUCKER: Okay. You guys have seen some of this data before, but I'm quickly going to go over the data that's in the analysis and then go to how it's changed with adverse events. Roger has gone over the disease burden that we have here in the first column. In the third column, you can see what's prevented by a national immunization program: almost one million cases of rotavirus diarrhea, which include 34,000 or about two-thirds of the hospitalizations and over 300,000 outpatient visits. The associated cost for that, as Roger said, is $264 million to the medical system and a full $1 billion to society.

For the rotavirus immunization program, we would get a cost effectiveness ratio of $103 per case prevented. That means you have to spend an additional $103 to prevent each case, including the hospitalizations and medical visits. That is the base case estimate of $20 per dose. To break even for medical costs, you need a $9 price for each dose of vaccine. From a societal perspective, we'd expect a savings of almost $300 million and a break-even price of $51. So as has been suggested, we included adverse events. Here's what I found in the literature. For fever after the first dose—from three different studies, quite a wide variety—the low numbers in the Rennels study are probably due to axillary temperatures rather than rectal temperatures being taken. The only one that was a significant difference between the vaccine and placebo groups was the Finnish study. The Finnish study was the only one that included outpatient visits and had a rate of 5.9 per 1,000.

For hospitalizations, we get quite a wide variety. You'll see from the two studies, we have a rate of .8 per 1,000 versus none in the placebo group, and in the Rennels study, an estimate that's off the charts—5 per 1,000. In the metanalysis, we looked at all placebo control trials. You get a rate of 2.0 versus 1.4 in the placebo group. For the safety and comparability studies, there was a rate of .6 per 1,000 hospitalizations in the vaccinees. Just to give you an idea, we looked at a baseline rate from the Vaccine Safety Datalink, which comes from four HMOs on the West Coast. It's about 2 percent of the U.S. population. We looked at all hospitalizations for any cause after immunization of DTP or DTP-Hib, and got a rate of 1.6 per 1,000.

Okay. So these are the estimates we used to update the analysis. The first column here are the estimates, the rates of fever, outpatient visits and hospitalizations with a sensitivity analysis range. These are the cost estimates. This is similar to the chart you saw before. The numbers in white are the results that we had from the previous analysis, and then I've crossed the ones out and put the number above that in

yellow—how it's changed when we included the adverse events. So you'll notice that there's a slight change increase in the cost of the medical program and a much larger increase to society. Most of the increase in cost of the medical system, the medical costs, are hospitalizations. On the societal end, the non-medical costs, most of the increase is due to fever. Actually, we included that a parent would miss one day of work for each case of fever, and one day for an outpatient visit and two days for an inpatient visit.

This here is a slight change in our ratio from $103 to $111 per case. The break-even price drops from $9 to $8. You'll see there's a slight change in our ratio, but we still saved although the cost of immunizing would not be offset by health care savings alone unless we had a vaccine price at $9 or below. Now that we've included adverse events, we haven't changed our conclusions, but it does shift the cost equation slightly so that the break-even point drops to $8 per dose. We recommend that post-licensure studies are needed to determine the accurate rate of rare adverse events, such as the hospitalizations. Thanks.

GLASS: Thank you very much, Andy, for that. So that's the update with the cost effectiveness. We can discuss that later on. Can I just have the slide on, please? Can I do that myself? Put on the slide projector, please. Okay. The next area of surveillance I want to cover is strain surveillance. This is from Jon Gentsch, Madhu Ramachandran and the group in our laboratory, who began looking at, a year ago, a surveillance of rotavirus strains in the United States much to my chagrin because I didn't think we would find much. Just to review, the serotypes of rotavirus are defined by the two outer capsid antigens: the VP4 and the VP7 that are on the outer capsid here. So we end up with having a dual system of P serotype and G serotype.

When we've looked in global collections and in the U.S. in general, we found serotypes 1, 2, 3 and 4 to be the most common and the only ones of real importance globally. So the tetravalent vaccine has been designed with these four strains in mind. After the vaccine development began, we conducted studies—surveillance studies of rotavirus serotypes in India—and found that this serotype 9 was highly prevalent and that serotype 1, the most common elsewhere in the world, was not found in this small surveillance that began our studies. Serotype 9, G9, was only present in India and Bangladesh with one isolate in Philadelphia ten years ago. So that was never a target or focus for vaccination.

Well, we began in 1996 with surveillance at ten cities around the United States that are marked here and with a pal of collaborators who provide specimens to CDC on an active basis. The results of the first year of

surveillance have just become available to us. While serotype G1 is the most common strain in the U.S. in the surveillance in ten cities, serotype 9, G9, we found for the first time in about 9 percent of isolates. These have not been in one city, but have been found in four of the ten sites. If you'll see in this yellow, 13 percent, 20 percent, 41 percent and 6 percent in Kansas City, Little Rock, Indianapolis and Omaha, suggesting that here, particularly in Indianapolis, it's a significant contributor.

When we look at the ten cities lined up, you can see the G9 in all cities. G1 is a common player except in Little Rock where we have a very small sample size. G1 is the most common type, but G9 in Indianapolis is the second most common type. In Little Rock, it's the second or third with small numbers again. It's certainly present in several other cities. So that as we begin thinking about introduction of the vaccine, we should monitor for G9 strains. The original vaccine studies with bovine strains suggested there was good cross-protection from one serotype to another. Although the reassortant vaccine studies suggest that serotype-specific immunity is important and protection is important as well, we really know how to assess this when the vaccine is introduced. I think it'll be something important to monitor, but this information has been made known to the major vaccine manufacturers and they're considering what to do next. Can I have the lights on and the slides off?

So that's the second feature. The third is that a year ago, we began looking at surveillance from a number of sites. One was the Vaccine Safety Data Link using data from Kaiser Permanente at four sites on the West Coast. What we presented at that time was data from the four sites where in these children who were monitored, diarrhea was the most common cause of complaint following vaccination. It had not been analyzed before. In the two years of surveillance, about two years of surveillance, there were 2,500 hospitalizations for diarrheal events in a birth cohort of about 70,000 newborns a year, and about one hospitalization per 25 children in the first two years of life.

From that, we went on to observe to, I think the surprise of many of the investigators, that there was this great peak of hospitalizations at the four sites: Kaiser of northern California, southern California, Portland and Seattle. A big peak of winter diarrhea hospitalizations that occurred each year; that these peaks also occurred in emergency room visits in all of those sites. The peaks in California occurred earlier than the peaks in Seattle and Portland, suggesting it was rotavirus. Using our traditional presumptive evidence of epidemiologic diagnosis of rotavirus, we said many of these are likely to be rotavirus. We made some estimates which were purely presumptive; you could believe us or not.

Since the data was presented, the people of Kaiser in southern California—Ken Zangwall, Joel Ward and that group—have gone on with funding from NIH and the company to look at surveillance and introduce rotavirus testing in ten hospitals, children hospitalized in ten hospitals, four emergency rooms and two outpatient clinics. We don't have a full year's worth of data yet, so these are preliminary data, but they've provided them to us. You can see that there have been hundreds of specimens screened. In January, about 50 percent of these were due to rotavirus. I can show you that in a different—these guys love color graphics and this is the rainbow curve where you see hospitalizations, ER visits and outpatients for about a nine-month period of time.

In hospitalizations, the purple columns are the totals. Over 50 percent of the hospitalizations where rotavirus was tested, specimen screen, had rotavirus as the causative agent. In emergency rooms, slightly less, just over 40 percent, and in outpatients, over 20 percent. This will come down when we get through the summer season, but at least it gives you an indication of the speculation that we made a year ago is likely to be true. We will now have a way to monitor impact of vaccine in a setting like Kaiser. It also demonstrates that the detection rates in the ER and in the hospital are roughly the same, suggesting that there may be a diversion of patients who would've been hospitalized to an emergency room because the proportion is about the same; whereas, children in the outpatient are likely to be less severe and have less frequent rotavirus.

So that's one follow-up study which hopefully could be used in the future to look at impact of vaccination, rotavirus-specific impact as well as hospitalization in general. The second study was a study from New York State. In New York State when we presented the data—we presented the data last year—they have over 10,000 hospitalizations a year for diarrhea with the same winter seasonal peaks that we've seen in the United States. They introduced rotavirus ICD coding in 1993. Since that time, have had about 1,000 children who have been coded with rotavirus. Yeah. Thank you, Joe. Here's the code; this is the figure. This is a study by Helen Cicerello, Yuan-dong Chen, Perry Smith and Dale Morris in New York State.

You can see again in about the 10,000, 11,000 hospitalizations for diarrhea a year—ten times what we can see in our national sample, half of 1 percent of hospitalizations—the same winter peaks of diarrhea hospitalizations not diminishing over time. In 1993, they began introducing rotavirus diagnostics. Now between 1993 and 1997, there were nearly 1,000 rotavirus-positive cases that have been ICD coded as rotavirus. We do not know if they're truly rotavirus or not because we haven't checked the record, but they appear to be rotavirus by coding.

In those children, seven children have died—about one in less than 200 of those who are hospitalized. These are really the first rotavirus diagnosed deaths in the United States. We have no ICD coding for rotavirus deaths now. That will be in the ICD kit 10 codes that come in a few years. So this is the first way we have to pick up rotavirus deaths. Let's just think again that the speculation we had about rotavirus from national mortality data is in fact likely to be true. We can begin to calculate rates here when we have more data available and data from more states. Similar data is available or total hospital discharges from 35 states. So we have a potent and robust way to monitor the impact of a vaccination program once it's introduced into a state and once coverage increases. With that—with those updates and vignettes—I want to introduce Joe Bresee, who's going to discuss risk groups for rotavirus. We've always been asked by this group if we can identify high risk groups for rotavirus. Joe has tried to identify risk groups from a variety of different data sources.

MODLIN: Roger, before we do that, why don't we just ask if there are very, any important questions for Roger or for Andy, or important issues, just one or two before we move on.

LE: Roger, one of the questions we had earlier was the rate of hospitalization in managed care versus the historical hospitalization rates. Do you find a difference in hospitalization rates? The second question, the New York data, you should look at the little blip of rotavirus versus the diarrhea. It doesn't look like it's the same as in Kaiser, which is 50 percent.

GLASS: With New York State, that data is really ICD coded hospitalizations. A new code was introduced in 1993. In New York State, only about 6 percent of hospitalizations for diarrhea are coded as rotavirus. Many hospitals do not use the code at all; some hospitals probably use it a lot. So it's a marker, but it's not a complete marker. In the Kaiser study, we've tried to get all hospitalizations screened for rotavirus. So that's part of the difference; is that's a compulsory active study as opposed to passive surveillance of naturally coded events.

LE: So was the hospitalization rates with Kaiser different than historical hospitalizations?

GLASS: The total hospitalization rate in the U.S. and in New York State for rotavirus—our estimate for rotavirus—is about 1 in 75, 1 in 78 children. For diarrhea in general, it's about 1 in 25 children. For Kaiser, hospitalization rates are slightly less. That was—the paper on the HMO is in press and will be out next month in *Pediatric Infectious Diseases*.

GUERRA: Roger, your data doesn't allow you to disaggregate from that populations of children that were in child care or by race, ethnicity or socioeconomic status?

GLASS: We really—we can't do that with national data. States like New York have great data on that, and in fact, have much more data per year than we have from a small sample. We'd be interested, for instance, in high risk groups, Medicaid, race. We can't get that from national data, but within the state, that should be available. I think Joe will address that in a specific study.

MODLIN: That's a good question because it leads right into Joe's presentation.

BRESEE: Can everyone hear me alright? One of the things, the recurring question I think at ACIP meetings and the working group meetings we had are can you identify—are there readily identifiable groups of infants who are at high risk for severe rotavirus disease, really hospitalizations? Our answer really, and other people's answer has been no. Though we all agree there probably are risk groups, there were very few data to support it. What I'll present you today are two studies which are unpublished, but the authors have allowed us to talk about their data that will address this issue and at least give you some information with which to make your decisions. I think what I'll do is I'll present the data and give you conclusions. I won't address the policy implications of the data because John's going to lead us through a discussion of that in a minute, but let me just show you the data to have you think about it.

The first study is a study called *Perinatal Risk Factors for Infant Hospitalization and Viral Gastroenteritis* done by a group at the University of Washington. What they did was a population-based case control study using a linked birth data—a linked data set which links hospitalizations for all infants in Washington State with all their birth certificates. So they looked at hospitalizations between 1987 and 1995, and they had three case definitions. Their main case definition was children less than twelve months old admitted to any Washington hospital with a diagnosis of viral gastroenteritis—really a very specific set of ICD 9 codes, much more specific than we use in our national surveillance.

They used as controls non-hospitalized infants matched by birth year in about a 1 to 5 ratio. They looked for risk factors that were available on birth certificates—really maternal and child characteristics that might predispose kids to being hospitalized. I'll just present the final data since we don't have much time. The table I'll show you has birth weight categories on the left side. Prematurity or low birth weight was one of the initial categories that we all talked about at the last meeting. It's been proposed as a risk factor for rotavirus hospitalizations. What's here are four categories of birth weight, fairly standard categories, and

the case definition I was talking about was here; that is all cases hospitalized for viral gastroenteritis. In fact, they used three case definitions.

To try to make a more specific case definition for rotavirus gastroenteritis, they only looked at, in the second column, cases of kids who were hospitalized in Washington hospitals between January and March—the time when you'd expect rotavirus in Washington State. Finally, they used a third case definition where only those kids who had an ICD 9 code for rotavirus specifically. As you recall, rotavirus ICD 9 codes have only been present since 1992, so there are really very few of those cases. What you see is that compared to normal birth weight category of kids here, that no matter what case definition you use, there actually are high risks for hospitalization, for low birth weight here and very low birth weight here.

You notice a couple of things. You notice that the magnitude of the odds ratios don't really change no matter how you bear your case definitions. There's very few cases over here, by the way, of rotavirus confirmed cases in the low birth weight—only three cases in this category. So the estimates are unstable. You see a dose response curve. The smaller you are, the higher your risk of hospitalization. The odds ratios don't tend to vary depending on what your case definition is. The next thing they looked at and we've been interested in is the relationship between low socioeconomic status and rotavirus hospitalizations. They found in fact four variables that were associated with hospitalization that were proxies or indicators of low socioeconomic status. These are low maternal age—moms less than twenty years old, moms who smoked during pregnancy, kids born to unmarried mothers and kids who are covered by Medicaid.

Again, what they found were that these were risk factors for viral gastroenteritis hospitalizations. Again, if you varied your case definition, you didn't change those conclusions too much. The second, the other point I'll make is that the odds ratios, though they are significant, are modest. The only other risk factor they found in this study was being a male. In fact, males were 42 percent as likely to be hospitalized compared to controls. Notice that the odds ratio is at least as high or higher than most of the low socioeconomic status indicators. They found several protective factors: including birth— when you were born—if you were born right before rotavirus season, you were protected; if you were born to an Asian mom, if you were born to a mom that was older than 35 or if you were a large child greater than 4,000 grams.

The factors that weren't associated with hospitalization were parity, other race and ethnicity, including black, Native American and Hispanic;

whether you were a twin or a triplet; whether you had necrotizing enterocolitis or another GI anomaly. The authors' conclusions from the study were these; that you could actually identify risk groups for viral gastroenteritis hospitalizations and probably rotavirus. The risk groups are what we all thought they were; that is low birth weight, maternal smoking, low maternal age, Medicaid, unmarried mothers and males. However, even if you could identify them, they were of moderate or modest magnitude for the most part. If you constructed a model where you tried to predict outcome, that is hospitalizations using these risk factors, the model was insensitive and non-specific. So it didn't—if you used the model to identify the kids who were going to be hospitalized, you didn't do much better than chance. In fact, to protect all children from hospitalization, you'd still have to vaccinate greater than 90 percent of the birth cohort.

Finally, the high risk groups account for a fraction of all rotavirus hospitalizations. If you lump their cases—if you look at their cases and lump all the high-risk groups together except for males, you'd account for 57 percent of the cases. If you looked at the most readily identifiable risk group, that is low birth weight kids, they only account for 10 percent of the cases in the study. One of the other groups that's been brought up in this meeting and in the working group meetings is Native American infants. That is a readily identifiable group that historically has had high rates of diarrheal hospitalizations, and a group you could actually target for vaccination. So what Bob Holman and his group at CDC did was do a retrospective analysis of discharge records.

IHS manages a hospitalization database which has all the hospitalizations in the Indian Health Service hospitals, tribal hospitals or community hospitals. Bob looked at all kids hospitalized in these hospitals between one month and 59 months of age between 1980 and 1995, and surveyed for all kids who had an ICD-9 code for gastroenteritis, again, using our standard surveillance gastroenteritis code, which is much more expansive than the Washington codes. Here's really the crux of the matter in this study; that the solid line here represents the rates of hospitalizations for gastroenteritis among kids served by Indian Health Service sites less than five years old. The dashed line here represents the data that Roger was just referring to, the National Hospital Discharge Data, which is the national data set that looks at hospitalizations in young kids in data we've presented before.

What you see here is that in the early 1980s in the beginning of the surveillance period, the rates for hospitalizations for acute gastroenteritis among Native American kids was about 2 to 2½ times the national rate. Over the sixteen-year period, it's come down to be pretty consistent with national rates. In fact, for the last five or six years, the rates have been identical. If you look at the actual data, this

looks just like the national data; that is this is the sixteen-year data plotted out by numbers of hospitalizations by age groups and the x-axis represents time—the year and month. What you see are these nice wintertime peaks. You see the wintertime peaks as the curve goes down. The wintertime peaks become blunted and the wintertime peaks were most prominent in the 4- to 35-month age group consistent with rotavirus epidemiology. More so just like national data, the peaks occur earliest in the southwest U.S., latest in the northeast U.S.

So you can take non-specific gastroenteritis data—the same way we've done with national data—and assume that the rates for gastroenteritis non-specifically as they've gone down reflect rates of rotavirus hospitalizations. So the authors' conclusions were the rates of gastroenteritis-associated hospitalizations in this population have declined by 76 percent in the last sixteen years, and that for the three years between 1993 and 1995—which are the three most recent years for which data are available—the rates were the same as the national rates. In fact, although the rates—but the rates remain higher still in the very youngest kids, meaning that a rotavirus vaccine program ought to be timely in this age group and given early. Because the gastroenteritis hospitalizations look epidemiologically like rotavirus, you can make the assumption that these data also represent what's happening with the rotavirus-specific hospitalizations. The authors' conclusions were that a selective exclusive rotavirus immunization program for this population may not be warranted because indeed they may have the same rates of hospitalizations as other American infants. That's all the data we have.

MODLIN: Joe, thanks.

BRESEE: Are there any questions?

MODLIN: Questions for Joe? Chinh.

LE: You know, in the first study, I'm surprised breast-feeding didn't stand out as a protective factor.

BRESEE: Well, breast-feeding wasn't looked at. That was one of the limitations of this study. It was all data from birth certificate records. In Washington State, evidently that data wasn't included, at least reliable on the birth certificate. So it wasn't one of the variables they looked at. It may be an important variable to look at; you're right.

LE: The second question is one of the slides should have birth weight less than 1,500.

BRESEE: Right.

LE: The rotavirus-specific odds ratio was 1.55?

BRESEE: Yeah.

LE: But only with a confidence interval of .32 to 5.9?

BRESEE: There were three children in that cell. So the estimates aren't stable, so I would ignore that.

LE: So we still can't make the case whether low-infant birth infants are high-risk or not?

BRESEE: Well, you know, I think that we can. I know that in all that data, the rotavirus-specific codes were only introduced in the last three years of the sixteen-year period of time, or the twelve-year period of time they looked at. There weren't many rotavirus cases. If you use the wintertime, the cases of gastroenteritis in January to March—which is really the time that rotavirus circulates in Washington State as a proxy for rotavirus—I think I can believe those odds ratios. I think that I wouldn't rely on the rotavirus-specific case evidence because there's just very few data, very few number, but you're right. We don't have any rotavirus-specific information. These are all proxies. Yes?

MODLIN: Any other questions? Okay, Dr. Gilmet.

GILMET: Was there any data in the first study on day care?

BRESEE: No, there weren't. Again, they only used what was available in birth certificates on large databases, so it wasn't available.

MODLIN: Marie? Fernando?

GUERRA: I guess the seasonal increase is also, I guess in a way parallels the seasonal increase for RSV. Were any observations made in terms of either co-existent or any current infectious illness, and/or hospitalizations that I suspect would be quite parallel?

BRESEE: You mean in the Washington study?

GUERRA: Yeah.

BRESEE: No; no. They specifically looked at only viral gastroenteritis codes and didn't pool anybody else.

MODLIN: Thanks. Let's move on. Dr. Margaret Rennels, Peggy Rennels, has graciously agreed to come back and consult for us once again. She's going to address the issue of taking another look at adverse events.

RENNELS: John asked me to review with you in a very brief fashion the reactions that have been associated with the rotavirus vaccine. Could somebody turn the light down please? The one reaction that has been consistently associated with the vaccine has been an excess rate of fever among vaccinees compared to controls. The rate of excess fever, however, has varied considerably from one study to another and let me review that. Shown on this slide are the percent of children experiencing a temperature over 38 degrees centigrade during the five days after the first dose of vaccine. I have put here five different efficacy studies, including the United States Multi-Center Trial at a one log lower dose than the other trials.

The licensure of dose or the dose proposed for licensure is 10^5, whereas this one was 10^4. The rates of fevers are shown in yellow for the vaccinees and white for the controls. Then the red bars represent the excess fever of vaccinees over controls. You can see that in the low dose multi-center trial, the difference was significant. It was also in the Finnish trial, and in the Venezuela trial and in the U.S. Native American trial. Actually, after dose two the difference was significant; even in the U.S. high-dose multi-center trial where axillary temperatures were taken. On day four, there was a significant excess rate of fever. All except this trial utilized rectal temperatures. So you can see that the excess fever ranged from lower than 8 percent in four of the trials up to 25 percent in the Finnish trial.

Now John Modlin alluded to some new data. Well, what he meant was the article published in the *Pediatric Infectious Disease Journal* a couple of months ago in which the Finnish investigators took another look at the reactions in their efficacy trial. In this new look, they looked at temperatures greater than or equal to 38 degrees. So they used a lower cut point and that increased the excess fever rate to 29 percent. The percentage of children experiencing a temperature greater than 39 degrees after dose one varied from 0 to 1.6 percent, and in the Finnish trial that difference was significant. Now again, they reanalyzed that greater than or equal to 39 degrees, and that increased the fever rates to 3 which increased the excess by approximately 1 percent.

The other thing that was brought out in the *PIDJ* article was other reactions occurring post-dose one. So what I have done here is shown the percentage of children experiencing anorexia, irritability, cramp and diarrhea or vomiting. In the Finnish vaccinees—in the Finnish control children—and in the U.S. high dose multi-center trial, the vaccinees in controlled children, you can see there were significant differences among the Finnish children for anorexia, irritability, cramping and diarrhea. Each of these, however, was significantly associated with fever. It was not an independent—it did not occur independent of fever.

In the United States trial, there were no significant differences in any of these reactions between the two groups.

As shown here are what data there are available on the reactogenicity of the rotavirus vaccine in 68 premature children who were enrolled in the rotavirus trials. In this column are the rates of diarrhea, vomiting, fever among the premature vaccinees versus to the premature controls. I have included then the whole cohort for comparison. You can see that there, yes, there are a few more children among the vaccinees who had diarrhea. There are a few more who had fever, but the numbers are very small and these differences are not significant. Then finally, I think it's important for you to be aware that the children who were enrolled in the trials were the big preemies. There were only four children less than 32 weeks gestation to our knowledge who were enrolled in these trials. The other thing I think that's critically important to be aware of is that these were all healthy children. None of them had had necrotizing enterocolitis, short gut syndrome, severe bronchopulmonary dysplasia, inner ventricular hemorrhage, et cetera.

MODLIN: Peggy, thanks very much. Questions or comments for Dr. Rennels? Chinh?

LE: I really don't want to split hairs, but just for the accuracy of what was code. I have to finish the *Journal of Pediatrics* April article here. Actually, when they dissected the fever greater than 95—I mean, 39 or greater, the fever rate in vaccinees was 3.5 percent versus .5 percent in placebo. It actually is a difference of 2 percent. I was a little bit more struck by that change than the. . .

RENNELS: Yeah. The difference increased by another percent.

LE: . . .yeah, than the previous *Lancet* article. The only reason I kind of labor on that is for the practicing clinicians, who at two to three months of age, you already have maybe to 3 to 5 percent of the kids who come in with possible bacteriemia or they have 5 to 7 percent of the kids who come in with febrile UTI, and then adding another 3.5 percent of a cohort who may have fever greater than 39. It's going to be a little bit of a management dilemma. Not always at that age you say, "Well, you've got the vaccine three or four days ago. That's likely to be the vaccine." It's just, you know, I don't want to labor on that, but I think it's when we present this to practicing pediatricians, it's going to compound on the question of whether vaccine. . .

RENNELS: There's no question that the vaccine is associated with fever. I think though that the rates are quite variable. I don't think that the U.S. rates are not going to be what we've seen in Finland, but unquestionably, it's going to happen.

MODLIN: Mimi?

GLODE: How tight is the timing of the fever in terms of its predictability?

RENNELS: It's pretty predictable. It starts on day four; it starts on day—some children will have it on day three; most children have it on day four.

GLODE: Okay.

RENNELS: And it's pretty. . .

MODLIN: And a few on day five in the Finnish studies.

RENNELS: And a few on day five, yeah, and it's brief.

MODLIN: Further questions? Peggy, thank you very, very much. This is, of course, a live vaccine which has not been tested in immunodeficient individuals—immunodeficient children—but of course, this does the beg the question of just what does rotavirus disease, the natural disease, do in immunodeficient individuals because it is a policy issue regardless of whether or not we have any information about the issue of the vaccine in children who may be immunodeficient. So at the request of a couple of Committee members at the last meeting, I decided to do a very limited literature review to find out what is known about rotavirus disease in immunodeficient individuals and have done so.

I've limited—the review was largely of interest in four groups: children with primary immunodeficiency diseases; both children and adults who are transplant patients, both bone marrow transplant patients and solid organ transplant patients; and finally of course, in both children and in adults who are HIV infected. With respect to the primary immunodeficiency diseases, there are a small number of articles in the literature that provide some useful information. They are listed in small type, but I'm sure it's not readable from the back of the room, but I'd certainly be happy to provide copies of this information a little bit later on.

I hope you can read the bolding. The primary immunodeficiency diseases that have been reported to potentially be a problem with natural rotavirus infection are largely those that are associated with profound T cell immunodeficiencies: severe combined immune deficiency, and cartilage hair hypoplasia. Interestingly enough, there's one reported case of persistent and severe disease in a child who had excellent agammaglobulinemia, which of course, is a disease for we feel—we think that the immunodeficiency is largely a B cell or at least a pre-B cell immunodeficiency where the children make no antibody, but presumably have normal T cell function or cell-mediated immunity. The

disease that occurs in the children with primary immunodeficiencies has been persistent and prolonged diarrhea with the metabolic complication, such as malabsorption that accompanies persistent diarrhea. Rotavirus antigen has been found in the stools of these children for long periods of time —the longest being at least fifteen months in a child with severe combined immune deficiency.

Interestingly enough, RNA analysis of the strains that have been isolated from the stools of these children on repeated bases have varied to the point where they suggest, at least in some cases, frequent reinfection with multiple strains of rotavirus. There are other interesting virologic phenomena that have been reported that I have not included for the sake of brevity. Also, it's been reported that rotavirus may possibly be disseminated in these children, and that the antigen has been found in serum of these children and also in hepatic and renal tubular tissue at post-mortem examination in a small number of children. I should hasten to point out that we have very little information or no one has really taken the time to look to see whether dissemination might occur in normal children, but at least we have some information that in some immunodeficient children, the antigen has been found.

I would point out also that there was not evidence of significant hepatic or renal disease that was attributed to rotavirus in these immunodeficient children. The second group were bone marrow transplantation patients. These are—there are two series that involve predominantly adults with a few children in them. They are both prospective studies. One was reported—the first one was reported, which is reference number 8 from Johns Hopkins and the reference number 7 is a prospective study that was conducted in France. Both of them found that within a few months after transplantation, bone marrow transplantation, that approximately 10 percent of transplant recipients acquired rotavirus gastroenteritis. The number was 9 percent, or 8 percent in one study and 11 percent in the other study.

Of the patients who did acquire rotavirus disease, the disease was associated with abrupt onset of fever, vomiting, diarrhea, but in both cases also, they found it was difficult to distinguish from acute gastrointestinal complications from all the other things that occur with bone marrow transplantation. Interestingly enough, persistent infection was not observed in this population of immunodeficient individuals like it was in the children with hereditary immunodeficiency syndromes. In the Yolken study from Hopkins, rotavirus infection was associated with longer hospitalization, with an increased risk of acute graft-versus-host disease, and with a strikingly increased risk of mortality in that the mortality—ultimate in-hospital mortality—in the group that was rotavirus-positive was about 60 percent compared to that 13 or 14 percent in those that did not have rotavirus disease.

Now this is overall mortality and is not directly linked to rotavirus infection, but at least pointed out that there was an association between the group that had serious rotavirus disease and the risk of dying in the hospital. There are only two studies that have addressed the issue of rotavirus in both children and adults with solid organ transplants. The first was a study in pediatric liver transplant patients from Pittsburgh; that's reference number 9, and then a second study on adults who were renal transplant patients. In both cases, there was some substantial risk of rotavirus disease occurring in immunocompromised transplant patients. The acute disease that was observed was more severe than that that was seen in controls and more prolonged. More prolonged, I mean that acute symptoms occurred for a mean of about 2.8 days as opposed to .8 days in the control population. Again, persistent infection was not observed.

Then finally, in the HIV/AIDS group, we have the information—the literature seems to be somewhat conflicting. There are both retrospective and cross-sectional studies from Sweden and from Australia which found a very high rate of rotavirus disease in largely adult men with HIV infection, for the most part had advanced HIV disease and were severely immunocompromised. They found that in one study, 14 percent and in another study 25 percent of these men who had unexplained diarrhea had rotavirus antigen in their stool. Their diarrhea was attributed to rotavirus. In the Swedish study, the rotavirus infection was associated with both severe symptoms and prolonged diarrhea lasting from anywhere to two to eight weeks. Even though the symptoms were said to be prolonged, all of the patients in the Swedish study were managed as outpatients.

On the other hand, we have three prospective U.S. studies, at least one of which was carried out here in Atlanta that involved a total of 207 HIV patients; again, mostly male patients with advanced HIV infection. All 207 of these patients had unexplained diarrhea and in none of those 207 cases was rotavirus antigen found. So this information doesn't quite comport with the information obtained that was from the Swedish and Australian studies. Roger may want to comment on that in just a second. I was unable to find virtually no information on rotavirus infection in HIV-infected children interestingly enough. There's one reported case from a group in Baylor of severe disease occurring in a child with advanced HIV infection where the infection occurred within just a few days prior to the time the child died. Otherwise, there was virtually no information about HIV-infected children and the rotavirus disease, which I find rather remarkable.

LE: Actually, John?

MODLIN: Yes, Chinh.

LE: There is in the *Journal of Pediatric Infectious Diseases*, 1994, an article from Africa—AIDS patients in Africa—in children, HIV in Africa, and they did not find an increase in. . .

MODLIN: Did not find it? Okay. I have to admit I missed that based on the literature search. Any questions about rotavirus disease in immunocompromised individuals at all? Yes, Neal.

HALSEY: John, to be consistent with the statement that I made at the last meeting, one of your former colleagues—Howard Letterman and other colleagues—have suggested that our statements with regard to live viral vaccines are too non-specific when we say "contraindicated in all immunocompromised." What would your thinking be about patients with chronic granulomatous disease and other white cell defects that are selective only as white cell defects where there's no evidence of increased risk of complications from viral infections? The point being is that some of the immunologists are encouraging us not to just blanket make statements that encompass every immunodeficiency possible: selective IgA deficiency and so forth. In places where we really don't know, then I think we may need to do that, but could we also include some language in the statement that indicate that patients with selective immunologic disorders have not demonstrated any increased severity of rotavirus disease?

MODLIN: I think your point is extremely well taken. We've actually discussed that, as you know, within the working group and have sort of made the decision that maybe beginning with this statement, that we could be a bit more selective in terms of precautions and contraindications regarding the vaccine. In fact, I think we have done so with this statement. We've tried to identify those that we consider to be at risk and then say that we will have precautions for children who are immunodeficient, who are HIV-infected.

HALSEY: But I think the language says "contraindicated."

MODLIN: We can and probably should be a bit more specific. That's the whole point in reviewing these data. Yes, Dr. Gilmet.

GILMET: John, as a follow-up to that, given the high prevalence of selective IgA deficiency, do we have any specific data on that entity?

MODLIN: No, not at all. Dr. Santos?

SANTOS: Just as a point, certainly the world over, moderate and severe malnutrition is the most common immune deficiency known. I think we

have to be very careful how we word this because certainly where the vaccine is mostly needed right now, it's in developing countries. Severe malnutrition, as you know, parallels or mimics very closely the immune deficiency variables in HIV. So I think we have to be very specific.

MODLIN: The point is well taken. You may remember in prior versions of the rotavirus statement, we included for our recommendation that the vaccine is recommended for healthy full-term children. We have, in fact, taken out that word "healthy" specifically for that reason so that it may be preferable to focus on those for whom we feel the vaccine is contraindicated and to be relatively specific about it. I agree fully with Neal's statement. Other comments? Okay. If we could move on, we'll try to do this very quickly. To the issue of provider acceptance, of course, this is an issue that arose in the midst of the discussion in February on policy analysis issues. One of the major issues was have we adequately pulled all the stakeholders or all those who might be stakeholders in developing immunization policy?

Of course, we hadn't and still have not, but what we have done is made an effort to get some initial pass at some data in terms of how practitioners—particularly pediatricians and family practitioners—may feel about the prospect of an introduction of a rotavirus vaccine. We're going to do this in two groups. I have a bit of data to present to you regarding electronic surveys of both pediatricians and family practitioners. Then Jeanne Santoli from the Immunization Program is going to provide some—show you some similar data from some focus groups that have recently been conducted.

The database here—or the data are admittedly quick, and dirty and relatively non-scientific. Let me explain the basis there. The same instrument, the same survey was sent to two groups of physicians to two different ambulatory practice networks. The first network, the PROS Network—P-R-O-S—is the Pediatric Research and Office Settings Network where we had some help from Mort Wasserman at the University of Vermont. The second group, these were—the PROS group were virtually all practicing pediatricians, most of whom who have some academic orientation, but nonetheless are practicing pediatrics in an office setting. The second group is the Ambulatory Sentinel Practice Network, which is largely a network of practicing family practitioners who received the same instrument consisting of about seven different questions.

The PROS sample was sent to 108 pediatricians of which we had responses after two weeks from only 36. Only about 33 percent responded to the survey. We don't have a denominator for the family practice group because of a technical glitch in that some members of the group sent it on to others or their friends. We got back responses

from individuals we didn't expect to get responses from. We don't know what the denominator in that case, but nonetheless, we had 44 responses for what it's worth. I told you this was quick and dirty. There were seven questions that were asked. The first was "as a cause of morbidity in my practice, rotavirus diarrhea is. . ." As you can see, these are the responses from—let's see if I can't; well, the heck with it—the responses from the pediatricians are slightly more than 80 percent considered rotavirus to be either very important or somewhat important practice; whereas, amongst the family practitioners, the response rate was somewhat lower, about 60 percent, considered rotavirus diarrhea to be important.

With respect to the desirability of preventing rotavirus diarrhea, the responses were similar. Close to 70 percent of pediatricians considered it either a very high priority or a high priority; whereas, only about 43 percent of all family practitioners responded in a similar manner. The next question was "if the Academy of Pediatrics Committee on Infectious Diseases and the CDC Advisory Committee on Immunization Practices stated that rhesus rotavirus vaccine was safe, effective and reasonable to use but did not make a recommendation for administration to all healthy infants, would you recommend and offer vaccine to your patients?" Here, we had 69 percent of the pediatric respondents said yes, they would; and 52 percent of the family practitioner respondents said that they would.

We went on and asked the next question, the obvious sequel, was that "if the vaccine were to be recommended for universal use as opposed to simply making a statement that was reasonable to use, if it was recommended for universal use, would you use it?" One hundred percent of the pediatricians responded that they would and 86 percent of the family practitioners responded that they would. This is complicated and I apologize. This was literally pulled off of the printer as I running out the door yesterday afternoon. We wanted to get a sense for those who answered no to the prior questions as to what—saying that they would not use the vaccine under—if they answered no to any of the prior questions, what the basis for not wanting to use the vaccine happened to be.

There were only thirteen pediatricians who responded to this because as you recall, most said that they would use the vaccine. There were 26 responses from family practitioners. The range of reasons for deciding that they did not want to use the vaccine varied considerably and there was quite a range. Some of the more important ones being that rotavirus diarrhea, that they did not feel or considered—or did not cause sufficient morbidity amongst their patients. There were some that considered it to not be sufficiently effective. Then there were a substantial number that stated that they did not feel that the potential

cost were justified. The other responses were less—there were fewer responses for questions, for opinions regarding the rate of adverse reactions and parental concerns about vaccine safety.

Then finally, the last question had to do with the seasonal aspects of rotavirus and the feasibility of administering vaccine on an accelerated schedule if it was considered desirable to do so, which may require additional visits for some infants. The question is "are you aware that rotavirus is seasonal completing a vaccine series amongst infants less than six months of age prior to rotavirus season would likely entail using an accelerated seasonal schedule which would in turn require additional visits? How challenging would it be for your practice to handle these additional visits?" Again, there's a range of responses from both the pediatricians and the family practitioners. I think the bottom line is that many considered that it would be rather difficult to bring these children back for extra visits. Again, I apologize that I don't have this material copied for hand-out. I can certainly make it available to you and will. It literally came across my desk at the very last minute. I'm going to pass the microphone on to Jeanne Santoli, who is going to give you some more information from her focus groups.

SANTOLI: Hello. I wanted to speak about some preliminary findings of a study that was conducted at the National Immunization Program. In preparing for a larger study to look at both provider and parental acceptance and understanding of rotavirus vaccine, we conducted two pilot telephone focus groups. One was a focus group of seven practicing pediatricians from seven different states across the country, and the other consisted of eight practicing family physicians from eight states across the country. The focus groups were designed to collection information in three main areas. The first was perceptions of the epidemiology and burden of disease. The second was concerns regarding specific aspects of the vaccine. The third was their support for recommendation of universal use of the vaccine.

I'm going to present some very preliminary observations. Just to remind you that this is qualitative research, so my words "some" and "most", that's as specific as I feel comfortable getting. In terms of the knowledge and perceptions, on average, pediatricians recognized rotavirus as a common cause of gastroenteritis. They stated that they didn't usually test patients for this disease. Most felt that hospitalizations among children were rare, but they did acknowledge that severe disease did happen with rotavirus gastroenteritis as opposed to other causes of gastroenteritis. Compared to pediatricians, family physicians were less familiar with the epidemiology. They also did not test frequently for rotavirus infection. On average, they spoke less about the potential severity of rotavirus gastroenteritis.

In terms of the specific concerns that the providers had, there were two that were commonly voiced: one was the high incidence of low grade fever and the anxiety that this would generate among parents. They were concerned that this would lead to a large amount of telephone calls and doctor visits. The second concern they had was some of the wide ranges for the efficacy data that are available, and particularly, some of the pediatricians were more concerned that they wished that the numbers were a bit higher. In terms of implementation, pediatricians were largely in support of the vaccine itself, but raised the question about whether or not targeted implementation might be possible. The groups they mentioned were children in day care or children—and this is vague—but children whose parents would be less able to handle an illness at home. Family physicians were a little bit different in terms of the implementation issue. They voiced significant concerns about the need for the vaccine in their practices. Several participants named other vaccines, such as HIV, hepatitis C and HPV that they felt would be more necessary than this vaccine.

Another thing that was sort of interesting was that we really encouraged providers to give us questions and concerns that they wanted CDC and the ACIP to know; and that we would bring this to the group of people who were thinking the most about this vaccine. Just some other issues that came up was there was a big desire on the part of pediatricians and family physicians to get information that they could understand about cost effectiveness. Then they had a lot of specific questions about storing the vaccine and why a diluent was required, and how long a reconstituted vaccine would last and what to do if the child spits up the dose. So they certainly had a lot of questions and that helps us to plan how we educate folks about this vaccine.

I think the implications for us at this point are at least three. First, that there is a difference between the way pediatricians and family physicians will receive this vaccine, or at least are predisposed to receive it. To optimize roll-out of the vaccine, we want to be cognizant of the differences and perhaps tailor some strategies for each group. Second, this pilot study brought to light some important perspectives, and questions and concerns that we think should probably be verified in a full scale focus group study and then quantified by means of a more generalizable survey of providers. Third, in listening to these groups, it seems that there's a need for the CDC to produce a clear, honest, easy to read description of the public health argument that favors the universal use of the vaccine. Optimally, this would be presented in various fora, either simultaneous with official recommendations or prior to if that is possible. I will—I have copies of what I've said here and I'll make those available tomorrow on the back table. I didn't realize the format, but in case anyone would want to have this in writing to be able to look at. Thanks for your time.

MODLIN: Thanks, Jean. Are there questions or comments about provider acceptance data? Chinh?

LE: I guess none of the studies seem to emphasize the question, "if the vaccine has to come out of your capitation to take care of this child, would you support it?" Do you understand what I mean? Would you say, "yes, I support this vaccine program, but I will send the kid to the public health to get it."

SANTOLI: That's a great—hello—that's a great question. That definitely didn't come up. We didn't target our questions that way. When they were asked about cost, nobody really thought it was a huge cost for the vaccine when we gave them the price range, but the question of kind of putting it in perspective—"if they had a limited allotment, how would they spend it?" That wasn't an approach that we used, but that's a really good approach.

MODLIN: Thanks. Neal?

HALSEY: Can we just ask what price range you gave them? Then a question for Chinh Le is when the varicella vaccine was introduced, it was a major problem with regard to capitation and reimbursement. It's also been brought to my attention if there's any we can avoid the conflict that occurred there, we should try with regard to reimbursement from HMOs and other insurance companies. At that time, three years ago now, there were a number of groups that had contracts with their providing organization that did have fixed capitation rates that did not have clauses that allowed for introduction of new vaccines that were recommended universally. Do you have any sense, speaking for HMOs and managed care in general—which we're asking you to do— do you have any sense of whether that's changed or that people have modified those contracts so that if new vaccines are recommended, they would automatically lead to an increase in the capitation? I'm asking both of you a question; I'm sorry.

LE: Well, I certainly can answer for Kaiser. Our policy has always been that if the vaccine is recommended, that we cover period. We don't even ask questions. So we were the very first one to use Hib vaccine; we were the very first one to use varicella vaccine and we really pushed it. So there's no question for us. If the national recommendation is to use, we will use it. The main question is not all managed care, not all HMOs are alike. I can't answer for the other ones. I know from my own family who don't belong to Kaiser, my grandchildren, they have to go get their varicella vaccine somewhere else rather than on their own insurance. So perhaps if there is a national law saying that if a vaccine is recommended for us, then the insurers have to cover. Then I think that

would be much better, but at this point, I can't answer for the other HMOs.

HALSEY: Let me just articulate it a little differently and maybe it's a question for CDC to get the data. A number of pediatric groups have told me during presentations that it is a huge problem when a vaccine is introduced because the dollars come out of their pocket because they have annual contracts that are fixed in price. Let's say the contract is fixed every October. If a recommendation is made in May, that means that the costs of that vaccine come out of their pocket between May and October when the new contract would come into place. I don't know whether or not these contracting mechanisms have been modified to state that if a new vaccine is recommended, the reimbursement would automatically be paid by this third party provider. It's one of the things that leads to resistance on the part of physicians who are now enrolled in these managed care kind of programs to accepting new vaccines. You didn't give me the. . .

MODLIN: Wait a second; I'm sorry. Did you want to respond, Chinh?

LE: Yeah. I know that with Kaiser we have a one-year grace period to introduce the vaccine. We renegotiate the fees and the premiums on a yearly basis. So we have a year grace period and then obviously, the premium is going to go up if the insurance is going to cover for the vaccine.

HALSEY: Can I just—I'm sorry, John.

MODLIN: Sure.

HALSEY: That creates a problem then if their expectation is you don't start until that time, it introduces a legal bind for the pediatrician who has a child with severe varicella who didn't get the vaccine or a child with severe rotavirus who didn't get the vaccine. We are creating a legal problem for them with the language that we write. I'm just giving you feedback.

LE: Right.

MODLIN: Right. Dr. Faggett?

FAGGETT: Yeah. Walt Faggett, National Medical Association. Speaking from managed care experience—both in Tennessee, D.C. and now here in Georgia—the cap rate usually is supposed to cover the vaccine. It should not, again, once the contract is negotiated, I'm sure Kaiser does the same thing. So it's assumed that that PNPM rate does cover it. So I don't think you'd have that much of a flexibility in response to a new

vaccine. That's not been my experience in a Medicaid managed care environment.

MODLIN: Thanks. Rick?

ZIMMERMAN: Another area or problem related to that is the ERISA plans, which they basically will do what they want to do as they are large companies that self-insure. So you even have the greater problem—you have a provider who may not be all that happy with the vaccine, and then he has to convince the patient to pay out-of-pocket because the ERISA plan won't cover it. That often occurs for some of the working poor since they could go to a federally qualified health center, but that means the provider is referring them out of their practice.

MODLIN: Right. Dr. Gilmet?

GILMET: John, let me make a couple of points speaking on behalf of the American Association of Health Plans. We have a proposal that's actually going up to the Board this year to endorse—to have the American Association of Health Plans endorse that all of their member plans support the ACIP recommendations. So I think that's a very important item. Secondly with regard to capitation rates, they're usually set at an annual basis. So it's important to know about what vaccines are coming down the pike so that they can be adjusted accordingly. To give an example, in our own health plan, we fully cover varicella vaccine. The reality is when we looked at the HEDIS data this year, only 20 percent of those vaccines were given so that pediatricians are actually being prospectively paid 100 percent and only delivering on 20 percent. Thank you.

MODLIN: Thanks, well put. We need to move on and we will readdress this in a second. At the request of a number of members—again from the presentation from the last meeting—we've been asked to conduct some sort of a policy review. I will admit up front that the working group has not either performed or commissioned a formal policy analysis, but I would like in the next couple of minutes to hope or try to demonstrate to you that we have followed a similar line of reasoning that might otherwise be followed by a formal policy analysis; we're comparing various options. Our ACIP Policies and Procedures Statement suggests the following steps in a policy analysis to verify, define and detail the problem; establish evaluation criteria; identify alternative policies; evaluate alternative policies; and display and distinguish amongst alternative policies.

I think it's fair to say that we've already done the—taken the first step very carefully and very clearly in that all of the information that Roger, and Joe and others have provided to you that help to define and detail

exactly what the problem is here. With respect to establishing evaluation criteria, these are the criteria that have been used. We've looked at vaccine efficacy. We've examined safety. We have made some attempt to estimate what the effect on overall mortality—I'm sorry, morbidity may be and mortality. We have certainly considered, as you have heard, cost effectiveness as measured by the cost of preventing morbidity. We have also measured whatever potential cost savings there may be in terms of dollars with respect to the cost benefit analysis.

These are the alternative policies that were—potential alternative policies that were identified by the working group. The options that we had were to make no statement whatsoever; say nothing about rotavirus vaccine. We could, secondly, recommend that the vaccine not be used. The language might be "rotavirus vaccine is not recommended." A third policy option was to recommend the vaccine only for high-risk groups. A fourth was to be permissive—a permissive recommendation in which the language might read "rotavirus vaccine is appropriate for all children." Then finally, the universal recommendation which would be "rotavirus vaccine is recommended for all children."

Now in an attempt to try to put these out and distinguish amongst them, we figured that we would really focus only on the last three recommendations for high-risk groups, a permissive recommendation and a universal recommendation because, of course, we didn't feel that we had an option to make no statement whatsoever, which we thought would be completely irresponsible. Secondly, this did not appear on the surface that making a statement advising against the vaccine made any sense as well. So that the only three policy options that really needed to be taken a closer look at were those for high-risk groups, permissive and the universal policy option. The recommendation for high-risk groups would almost certainly have the least impact. If we were to immunize high-risk groups only, it would have the least impact on overall morbidity.

The cost benefit and cost effectiveness might be slightly higher, but not substantially higher than the other options. That's based on the information that Joe recently showed you; that if we could identify what high-risk groups are, such as children who are born prematurely or children who come from only certain socioeconomic backgrounds, we might have a slightly higher cost effectiveness based on the fact that we could prevent a slightly larger number of hospitalizations. As you saw, the relative risks were relatively low. So that whatever difference there may be between this option and the other options is likely to be small at best. The relative risk to the normal population is only modestly larger or only modestly higher.

Also, the high risk groups, as you've heard, are relatively difficult to define. We've made some attempt to define them based on the data that Joe presented to you from Washington State and from the Indian Health Service. I think as everyone in this room would admit, even these data are still somewhat soft. We don't have any precise information on what definition there may be for high-risk infants. Currently we have, as you heard, very little data on safety and efficacy of the vaccine for premature infants as well. What information we do have is the information that Peggy just presented to you. With respect to the permissive recommendation, we'd expect that the reduction in morbidity would be directly proportional to the immunization rate achieved. We don't know what that immunization rate might be.

Based on the very quick information that we had from the provider surveys, if there were a permissive recommendation, we might achieve immunization rates of 60, 65, 70 percent. That's just a very broad estimate. The immunization rates would almost certainly be lower than with the universal recommendation. The cost benefit and cost effectiveness is likely to be similar to the universal option. Here, the idea is that we don't expect with this particular vaccine that there would be—since this vaccine, we wouldn't expect it to provide any significant degree of herd immunity of any sort; therefore, whatever benefits there are are the benefits that the child and their family, or accrue to the child and their family and do not extend to others in the population. Therefore, cost benefit and cost effectiveness for the permissive recommendations is likely to be not a whole lot different than it would be for the universal option.

The advantage of the permissive recommendation is it does accommodate provider and parent choice, which we consider an advantage. The disadvantage may be that the vaccine, as we've stated, may not be covered by some states, by HMOs, by third party pairs. In fact, with this option, there's certainly the possibility—the possibility—that in some cases the availability would be restricted to those with the ability to pay. Finally with the universal recommendation, you would expect that there'd be the highest reduction in morbidity. Again, the cost benefit and cost effectiveness is likely to be similar to the permissive option. The availability of vaccine would be the highest with the widest access. The singular disadvantage that we could identify is it is perceived as a mandate and raises some of the issues that have been raised with this last discussion that Neal and others have raised. That's it. I think this is probably an opportune. . .

RABINOVICH: Would you clarify. . .

MODLIN: Sure.

RABINOVICH: Would you clarify the implication of universal to mandate—universal recommendation implies how broadly the ACIP is making the recommendation? The mandate does not—is that not a state-by-state decision whether a vaccine is mandated?

MODLIN: If vaccines are—John, do you want to address that?

SNIDER: That's correct. I mean, it's the states that make the decision with regard to, let's say, school entry laws or what have you for any other group.

RABINOVICH: That's a mandate.

SNIDER: We do have to admit though that some states have in their law that they automatically adopt ACIP recommendations. I know Pennsylvania does, but most states don't. Most states make the decisions on their own. I think what people are saying is that there is something to this effect. I mean, clearly there is no mandate from the ACIP. It's a set of recommendations, but they are along with the AAP recommendations, are given high regard and find their way into standards of practice, if you will, both by state laws, by professional society expectations and so forth, and therefore, in an indirect way, have an impact on the situation that was pointed out earlier, for example, where if someone does not follow an ACIP recommendation which is widely adopted, say, within a year or two after it's announced, that they may be under certain circumstances at a disadvantage if there were some kind of legal action that was taken. John, do you want to add anything else?

MODLIN: No.

LIVENGOOD: Well, I think that's—excuse me—very true in general, but not true at all in this specific circumstance of rotavirus vaccine for a couple of reasons, one of which you can't give it over one year of age. So what are you going to say to a child whose three, four or five on school entry; that they have to take a vaccine that's contraindicated? So I think there'll be no effort to include this in state immunization laws and regulations. Similarly, we'd used HEDIS in some of the earlier discussions about this. I've been, you know, in the room with the Committee on Performance Management when they vote on these things and I've worked on implementation things.

The way this particular measure works for two years old, you can't—you'd only have to have been in their practice for twelve months. Again, they're not required to give a dose after one year of age. So I don't think it would make an effective HEDIS measure at all. I'd be really surprised to see any movement on that regard. Remember for instance, that the HEDIS measure for Hib is one dose. Seeing that you

get a child at twelve months of age, the only applicable dose is the one booster dose to that child. So that's all you can be held responsible for—not what should've been given at a previous health plan at two, four and/or six months of age. So those are very clear reasons why HEDIS in particular, in this particular situation, but as regards to what you were saying—let's say three years from now if you're not using this vaccine and it was recommended for universal, I think you would be at some risk of not complying the standards of care, which are in some ways set by AAP and ACIP in the vaccine field.

MODLIN: We'll go around—Chinh and then, okay; go ahead.

LE: I guess one of the hardest things to sort out is what level of cost effectiveness you're talking about. Whether it's cost effectiveness in terms of equal savings in medical costs versus cost effectiveness for society savings. It's, you know, if we had all the money in the world, we could afford this vaccine. I guess we can afford this vaccine if you're talking about formula in children. Even if it is $100 for three series—even if it's that—it's only probably half the cost of B-2 bombers. So society does have priorities in terms of paying for this. On the other hand, at the insurer level, I think it's a big issue because insurers are kind of playing the money in terms of whether they are obligated to pay for indirect costs.

SNIDER: We have an agency policy and that is to take the societal perspective in terms of our agency decisions. That is not to say that we don't take into account other perspectives and that these other perspectives aren't feasibility issues in terms of implementation, but in terms of the agency's—in fact, we had discussions with our ethical advisors about this. The bottom line is that as a federal agency, we really are obliged to take the societal. . .

LE: Sure.

SNIDER: . . .perspectives as the standard by which we would look at these things and look at the relative cost effectiveness since it's always relative.

LE: Yeah.

SNIDER: But the other perspectives are more feasibility issues, if you will, because they represent potential obstacles if certain stakeholders wind up spending money who have to act, you know, wind up spending money on the program. We have to recognize that and find ways to overcome those obstacles.

LE: As an agency, but for private insurers or managed care, they don't have that—they're not mandated to look at society's cost, do they?

SNIDER: No, they're not mandated although there was, by the way, a national conference in which the cost effectiveness experts in the United States and overseas, by the way, made a strong plea that everyone who does cost effectiveness analysis and everyone involved in the health care system take the societal perspective into account.

MODLIN: Okay, Dave.

FLEMING: I think this issue around cost effectiveness is one that may in the future warrant a more general discussion. It's going to come up big time tomorrow when we talk about Lyme disease vaccine. I guess the question I'd like to put forward is whether when we're talking about cost effectiveness, we mean cost savings or not. For most conditions, we're talking about cost of that void or cost per quality life year. I think that even a perspective that says that this needs to be cost savings from a societal perspective may be too stringent a standard for a vaccine utilization, but I think it warrants a more complete discussion at some point.

MODLIN: I did want to make the point that we didn't really make a—we didn't feel that there was likely to be a major—obviously, distinguish between cost effectiveness and cost savings with respect to the thinking here. We just didn't feel that for either one of those measurements that there's likely to be major differences between one option and another with respect to either one; there probably will not be. So those two characteristics were not useful in distinguishing between the most likely vaccine policy options. Fernando?

GUERRA: Yes. An ACIP policy recommendation for any one of these strategies would then imply that in the future, this would be a consideration for VFC coverage. Is that correct?

MODLIN: Almost certainly, yes.

GUERRA: So that would certainly help to, at least in the instance of having provider/parent choice, would help to offset the dilemma for some parents that are eligible because of not having coverage.

MODLIN: I don't think there's any reason why if we did not have a universal recommendation, if we had the permissive recommendation—and we've said this before—that there certainly would be a consideration that the vaccine could be provided to VFC. I guess the major question would be would the same thing be true for HMOs and third-party pairs—the private third-party sector. That's the question that I think is very difficult to answer. You actually run into a situation where you might run the risk of having those who come from more advantaged backgrounds be

more likely to be immunized. That would be the one setting where you might actually do your cost effectiveness and cost benefit if indeed that were to be the case. I didn't make that point before because we obviously have no information to substantiate that. I think that's a bit of a risk to the permissive recommendation. Maybe this is a good point in time to ask, actually Dr.—well, go ahead Dr. Graydon.

GRAYDON: Yeah.

MODLIN: Mr. Graydon, pardon me.

GRAYDON: One thing I would like to add is that if it is a universal recommendation of ACIP, then Medicaid must cover it in the APSDT program as I'm sure Barbara is aware of. Then it would be a burden on the state, and I'm talking about a mandate if you will, unless VFC then follows up and covers it.

MODLIN: Right. Dr. Ganiats from the American Academy of Family Practice did ask to make a statement. This would be an. . .

DEBUONO: Can I clarify the permissive language because I'm not sure I followed your logic on that.

MODLIN: Sure, Barbara.

DEBUONO: If the language is permissive and we went on and made a VFC recommendation that potentially you might have children in Medicaid and in child health insurance expansion programs covered for a vaccine that in the private sector, commercial insurance companies may not cover, therefore, having the opposite effect.

MODLIN: Well, perhaps that's the case if all children who would be considered to be at a slightly higher risk would receive a vaccine through VFC. Presumably most would, but for those who might come from lower socioeconomic backgrounds who may be covered through non-VFC programs, there may be some—the vaccine would certainly be available to them if they were to go to the public health clinic or what-not, but yes.

DEBUONO: Yeah. I just think that would create a certain level of disparity that I don't know that we want to be responsible for promoting.

MODLIN: Right, right. Since we're uncertain about that, that's why I didn't make a point of it during the presentation, but it was certainly a consideration. It was a point that was brought up during the policy option discussions.

GANIATS: Thank you, John. My written comments that have been distributed, they'll be modified somewhat because of the discussion that's already

occurred today. I appreciate the opportunity to talk. I'm representing the concerns of the Commission on Clinical Policies and Research of the American Academy of Family Physicians. It's that Commission that is responsible for making recommendations to the AAFP Board of Directors on immunization policy. Obviously, there are a lot of issues that we agree on. Several of these are that financing of childhood immunizations is a key concern for many constituents. The rotavirus infection is a common problem. It causes significant morbidity and some mortality; that the vaccine can effectively reduce the burden of the disease and that it is appropriate for a large segment of the population. On the other hand, we don't believe that at this time, the universal—and these, I'm very happy you brought this hand-out or slide because I didn't bring any and this is appropriate—but the universal recommendation status is appropriate at this time.

I'd like to make a couple of comments about why we actually prefer the permissive. First, the mandatory nature of your recommendations are real life. Recently, Dr. Livengood might not know this, but it's the CPM of HEDIS just earlier this month approved a recommendation— I mean, approved a measure that isn't every two years, a once in two-year measure. So that there is precedent to evaluate something that would occur in the two-year time window, so this could happen. The AAFP supports, as I mentioned before, patient-centered, evidence-based, but also thinks that patient preferences are very, very important. Patient preferences, of course, can be overridden when societal benefit dictates, such as herd immunity or a major cost effectiveness benefit that we don't believe occurs here. When those do occur, then it would be appropriate. It makes you wonder whether or not the societal justification to override patient preferences exists.

We're very concerned about the economic leverage that you'll give to a drug manufacturer by recommending a universal immunization or approving an immunization before a final price has been set; and that while most patients may benefit from it and most patients may not like it, we don't think that the data is there yet to support this. There's two points I'd like to make, expand on a little bit. One of them, the concerns about patient preferences, or in this case parental preferences, extend just beyond the academic and the philosophic. The real potential, the decreased acceptance of all childhood immunizations or a series of childhood immunizations is a serious concern. We have to ask ourselves about the question about opportunity costs about each additional vaccine. This cost has to come from two different lights.

First of all, what decrease in overall vaccine—childhood vaccine, acceptance or compliance—will be realized with each additional vaccine that you approve? That's particularly important in light of the large number of childhood vaccines that are in the pipeline right now. Given

that there could be this decreased compliance, which vaccines that are in the pipeline should be considered to be the most important. The rotavirus is a particularly challenging issue; I agree because those at highest risk for the disease may be those who are the lowest—at the highest risk for the lower compliance. That gives them interesting balance for your Committee to consider. The cost issue is the second one I wanted to expand upon. We've already discussed it a bit and I agree with your comments 100 percent.

We don't believe that the issue has been fully explored at this time. Though I appreciate some of the pilot data that was presented, it's still just piloted data. We feel that there's little reason to rush to recommending a universal recommendation at this time for the vaccine. In fact, I feel we've got to be contraindicated except for, perhaps, the high-risk groups for your consideration. This gets us to this idea of how can you have the permissive and still have the insurance companies paying for it? VFC is nice; okay, you can arrange for that, but—and this is where I don't have the background that you have—but to have language that allows permissive or approved vaccines still funded by insurance companies would be critical. Patient preference, provider preference, patient acceptance is going to be key for this in working with patients, and providers and then the insurers. To help support the patients' decision, I think is important. Thank you.

MODLIN: Thanks, Dr. Ganiats. We shall continue. Additional comments? Sam.

KATZ: I think there are a lot of questions that have been discussed very appropriately. I'd just like to put two other slants on it. One of course, in relation to the remarks you've just heard, the slide you saw earlier today from Jose Cordero, we're getting further and further away from oral polio vaccine in the first months of life. This is not another injection; this is another feeding vaccine. It's a mucosal immunization, not an injectable one, so I'm not as concerned that this is going to make the immunization schedule so complicated or so unacceptable to parents. If their child has to ingest something rather than having another injection, I think that's fine.

Another issue which doesn't face quite the same as the health maintenance organizations, but there are fifteen at least and maybe there are more now. Jose, you'll have to tell me of the fifty states, which are universal states. They provide all vaccines free no matter what your immunization coverage is under insurance, or Medicaid or anything else. We have to go back and deal with our state legislatures when it comes to whether there will be funds to cover the gap between what the federal funds may supply and what the state will then have to add to it in order to apply universal immunization. I don't think that's a challenge that we're unwilling to face. We've done it with varicella

zoster; we've done it with hepatitis B. Here, as you've pointed out, here is a vaccine that's not for ten birth cohorts of 40 million children; it's for one birth cohort per year of 3½ or 4 million children.

Finally, when Barbara DeBuono talks about disparity, I agree with her. I've been waiting for Roger Glass to get up and yell, you know. If we're going to discuss Lyme disease vaccine, which is as "yuppie" a vaccine as I've ever heard of, this is a democratic vaccine. We shouldn't be talking about how we can afford to give it in the United States. How can we give it globally where we have 400,000 or 500,000 deaths a year from rotavirus? So I think our focus—I realize ACIP is not responsible for the rest of the world, but I'd love to see that slant, at least that perspective in people's minds.

MODLIN: Thanks, Sam. Chinh?

LE: Just along the lines that this is a democratic disease and a democratic vaccine, if we were not to have universal immunization, but have permissive immunization, again, segments of the children population will not get it. Maybe the very poor would get it through the Vaccines for Children Program. The very rich can get it because they don't— they have the money. The middle class or the poor working class may not. So I think it's really an ethical issue in terms of if we were—if we have this vaccine, we really have to offer it to all the children and not just in the permissive way.

MODLIN: Marie?

GRIFFIN: I'm still a little concerned about the safety issues. I think, you know, we've seen that when things are recommended for universal immunization, for varicella, they don't get—there isn't an immediate uptake. I mean, people do it gradually, which I think is beneficial. I wonder if we could just put some wording in the document to indicate a level of concern or to appreciate people's concern about using a vaccine that hasn't been used in tens of thousands or hundreds of thousands of children in the U.S. so that someone isn't—this recommendation, we aren't, we don't feel like we're pushing it down people's throats who feel uncomfortable with it, and that there may be a few years when people say, "Well, I'm just going to wait and see what happens." I'm just wondering if there could be some language like that in the recommendation.

MODLIN: Do you think you could suggest some off the top of your head that would be appropriate?

GRIFFIN: I mean, I think, yeah; I mean, I think if I sat down and I'll try to do that. I guess my feeling, and I'd like to hear other people's, would be some

practitioners and patients, parents may elect to wait until this vaccine has been in use for one to three years prior to using it in all children or something to that effect.

MODLIN: Barbara?

DEBUONO: I think gets back to an issue that I think we may have raised at the last meeting that was troubling to some of us, and that's this notion of moving forward on a statement, which then on the heels of that statement would be a VFC recommendation without the vaccine's official approval and a price being set. We're still in some ways in a similar position to where we were before, although I certainly think that more work and more information has come before us regarding the studies on cost effectiveness and the New York information as well. I don't know how to deal with that issue; that it's not been approved yet and that we don't have a price. I continue to be troubled by that. I don't recall historically whether or not we have approved a statement and approved a VFC recommendation without knowing those two things.

MODLIN: Right.

DEBUONO: Maybe Dixie, you've been here awhile. Also maybe you can refresh my memory.

SNIDER: Yeah.

DEBUONO: I don't know how to deal with that issue still. I'm still troubled by it.

SNIDER: Well, I think first of all, you haven't made a recommendation to CDC as of yet. CDC hasn't yet accepted your recommendation. We certainly are not going to ask for a VFC vote today on rotavirus unless somebody has changed the agenda.

DEBUONO: But what I'm saying is that it frequently follows quickly the statement recommendation when we put it in the statement and we say we're going to recommend to the CDC, et cetera. I have not seen it where we don't also then subsequently make a VFC recommendation as well. So I think we have to think of approving the use of this vaccine in the context that we will likely move down the road of a VFC recommendation as well. I don't think we should separate the two things at least in our—we may not vote on both today, but I certainly think the implications are that that's the road we'd be going down.

SNIDER: Right, that's correct. Also for everybody who may not be familiar with the history though is that I think we have tended to make our recommendations as broad as we feel are appropriate. Many of our VFC votes have been more restrictive than the broader idealistic goal

we have with the recommendation because we take into account in the VFC—we've taken into account in many of the VFC votes a lot of the feasibility issues that have been discussed today. So that, you know, these issues come up again a second time when you go to a VFC vote and in some cases temper, you know, what the VFC vote is. That winds up being somewhat different than the recommendations on some occasions.

In this one though, I agree. I think it's much more problematic because many of the times what we've done is to try to hit certain cohorts. Even though we made a broad age group— recommended it for a broad group—when we've gotten to a VFC vote, in order to make it feasible to implement, we've taken certain cohorts and said VFC covers this group and that group. This one is not going to—we certainly aren't going to chop it up like that. So I think it's true that what we say in the recommendation here will probably have to be fairly close to what we say with the VFC vote.

MODLIN: Rick?

ZIMMERMAN: In terms of evidence-based, patient-centered medicine, one of the issues is whether you use conditioned proxies to override actually giving parents a choice. You do that often if the disease were to society—and particularly if there's high disease, mortality and a very safe intervention. I guess a couple of issues. This is clearly a disease of short-term morbidity chiefly, not long-term morbidity or mortality, and there is with the first dose—but only the first dose—there is this issue of fever and potential for febrile work-ups. So I guess I—does that, you know, do we—with this disease and this vaccine—do we have that information? So I don't think we do, but I do think we have a concern from the inner city based on the data presented earlier. There may be yet one more option that you don't have up there. That option would be a permissive recommendation generally, but a stronger recommendation for persons of high-risk—in essence, combining the first two. So that might be a way to protect those at highest risk while giving more permissive recommendations to others.

MODLIN: Paul?

GLEZEN: Maybe I'm wrong, but in the family practice statement and what Rick just said, I sense there's what I would consider a misunderstanding of what a recommendation would be. They used the term "mandatory" and Rick just said "overriding the parents' wishes." I don't think a recommendation for universal immunization is either of those. It's not mandatory and it does not override the parents' wishes about this. So to me, mandatory would be if you had a school entry law requiring immunization. From what Sam just said here and in thinking about this,

I don't think that will happen with this virus because this is not a disease that carries over into that particular age group. So this is unique in that sense. I think that have to think of a recommendation that's just saying that we think this is the best thing for these young infants to be protected. It's not mandatory and it's not overriding parental wishes about the use of this vaccine. They'll still have a choice. I think that overall as a pediatrician, we have to be advocates and we have to think about just the problem of putting a baby in the hospital. I mean, just that very act of hospitalization is a deterrent to good normal development. I think that anything we can do to prevent that, we should do.

ZIMMERMAN: Perhaps "overriding" was the wrong word.

MODLIN: Okay. Mimi?

GLODE: I just again want to think for a minute about the issue that, well, I at least am having trouble with. I think it's one Marie also has brought up; that is, you know, upscaling essentially from thousands of children to millions of children and taking a very small risk of a vaccine that when translated up to millions might not be as safe, or have some adverse effects that we don't know about or might not be as effective or something. So I guess the issue is is it just like "wimping out" to have some, you know, probationary status where a vaccine that we recognize that we're scaling up from thousands to millions, and we recognize that there might be something we're missing? So there is a 12-month period of time, a 24-month period of time—something— and a lot of pressure on post-marketing surveillance to have this probationary recommendation which is then revisited twelve months later when the, you know, four million information is presented and the Committee then endorses, you know, officially a universal recommendation or something.

MODLIN: I want people to understand that the reason why I've been trying to at least push things along here is with the realization that recommendations from this Committee do evolve slowly. They take a long time to be published and a long time to become "official policy" of the CDC. It seemed to me to be irresponsible for us not to be moving on the issue and at least to have some direction that can— some information that we are going in a certain direction that can be provided to practitioners at the time that this vaccine was licensed because you can imagine what—"chaos" may be not the right to use, but certainly "uncertainty" once the vaccine is licensed, is marketed. The detail representative shows up on a door step and says, "Here's this vaccine. It's safe and effective and you can give it by mouth," and the practitioner turns around and says, "Who do we give it to and how do we use it?" That's why I've been trying to push things along. I do feel

that it's the responsibility of the Committee to have a very clear sense of where we want to be. Even though we may not have a set of published recommendations and almost certainly won't, and almost certainly will not have a VFC resolution at the time that this vaccine is licensed. So I see this as an evolutionary process—not something that has to be done right away.

SNIDER: There's also the issue of the natural uptake or diffusion of innovations that people should keep in mind. This is not speaking for or against what you're saying, but you know, I think it's been known for years and some people have written long books about how slowly new innovations are adopted, and so that we're not talking about the whole cohort. We're not going to get there. In fact, I think the varicella is a good example of, you know, of what the uptake will be. So I question, I think, what you're raising is "Do we want to put additional breaks on what would be a normal uptake process, which would take several years to reach very high levels?"

MODLIN: Marie?

GRIFFIN: Maybe it would be an additional break, but I think there just should be language that says we recognize that this happens and this is appropriate. So that people who really feel uncomfortable don't feel like we're cramming it down their throats. Maybe it would put a break on it, but I think that maybe we could work on some language that says "This is the natural course of things. This is probably appropriate and there are plans." I think if also we knew there is post-marketing, what post-marketing surveillance was in place, et cetera, I think a more formal type of "we're going to revisit this in one year or two years" makes a lot of sense.

MODLIN: Sure. Okay. So Marie, you would be prepared to vote for a universal recommendation today so long as there was language in the statement to the effect that "some practitioners may consider it reasonable to wait on the basis of personal choice"—something to that effect?

GRIFFIN: Right.

MODLIN: Chuck?

HELMS: I've been sitting here trying to articulate in my own mind an argument here. I think I'm coming down on the side, but I really don't see any other way but universal immunization. We can't define the high-risk groups and there's an issue of equity with permissive that immunization in this society where people—some people can afford it and some can't. Some people who could afford it might want to do it and if it's not recommended for them, why can't they go ahead and do it? I think

you've got a problem with that. I think the universal recommendation is going to be the only practical one that you can come with.

In hearing the arguments about opportunity costs, at first they struck home pretty hard to me. I'm thinking of potentially throwing the baby out with the bath water in the sense of good immunization rates for some very important vaccines which we have out there now. Losing that rate because we add another one, I guess, is an argument. To me, the fallacy, however, in the argument is that you don't know really where you are yet. Is it the responsibility of this particular Committee to determine where we are with that argument? I don't think it is the responsibility of the Committee. To do it in a, if you will, prospective fashion because I don't think the problem will be solved prospectively. I think the stress has got to be the—people have got to see what the cost implications are; the fact that maybe the cost implications are threatening the system a little; that maybe the immunization rates are suffering a little bit before people are going to take any problem like this seriously.

To hold up here, at this particular point in time where you don't know what the effect of this vaccine is going to be on the entire immunization system, country, is probably inappropriate. So I guess I'd be sort of for "mushing on" and pushing forward with this and getting it done and marketed. I'm also concerned, frankly, about what either of the other two decisions would mean to the vaccine manufacturers, and particularly a vaccine like this that has worldwide implications versus one that, for example like Lyme disease, which also has worldwide implications, but right now, the disease hasn't grasped the world's attention the way diarrhea can with its—particularly if it's mortality worldwide.

MODLIN: Okay. Fernando?

GUERRA: I would also support, as a matter of record, the universal strategy, but I suspect if it was implemented, it would become very much of a permissive one. That's what's going to give us the opportunity to really address the concerns that Marie has—is I think the post-marketing implementation efforts take place for surveillance. I think that, you know, we have some precedent in the way that Dixie referred to varicella. I think it was, you know, the observation after it was out and much broader implementation that there was a group of kids who were very susceptible to the complications and it was then that came back to this Committee. I think the same thing with hepatitis A. When we initially passed the recommendation, it was without so much consideration being given to the different categories of at-risk individuals from low, intermediate and high. As we have had a chance to see how that can be implemented in communities, and especially

with the support from VFC, it can be a very effective way to make those observations.

MODLIN: Alright. Thank you. Yes, Carolyn.

HARDEGREE: I think this discussion has also pointed out that it's going to be important to be certain that there's data to support everything that's in the statement. We, I think have heard several times that we may not have had data in populations of ages greater than the six months or the 32 weeks—36-week period. We need to be very careful about extending into time periods for use that we may not have. Secondly, even though it's listed that we may have information in the evidence table about all the simultaneous immunization, I would ask that you be very careful about what data we have with U.S.-licensed products in any of these that go into the table.

MODLIN: Are you uncomfortable with the current language in the statement regarding premature babies? In other words, it is listed as a precaution.

HARDEGREE: Well, I think it's more the issue. . .

MODLIN: Okay.

HARDEGREE: . . .of the older child. . .

MODLIN: Okay.

HARDEGREE: . . .and when you give the second and third dose, and how far you can go beyond the use of the first dose that people at FDA have not seen much data on this point.

MODLIN: That issue has come up with the working group and it has been discussed—the fact that the recommendation does seem to extend beyond what trials. They address ages of children for which the trials have not provided data to address the issue. On the other hand, there's some very important practical issues that a committee like this has to face with respect to recognizing that not all children are immunized on exactly at two, four and six months of age, but that question would come up. There's no doubt that that issue has certainly been discussed, Carolyn, and in considerable detail within the working group. There's no doubt about that. Rich?

CLOVER: Following up on your comment, I want to first say I appreciate your comments and disease reanalysis in the last ACIP meeting. The one question reviewing this before coming that I had not seen before was the minimal interval of time being three weeks. I don't have knowledge of that data to know that that's an appropriate minimum. I raise the

issue, not per se from a vaccine efficacy issue, but a compliance issue. The other live vaccines basically have a four-week interval of time. We've seen that this provider adherence accelerated schedule is confusing as it is anyway. Is this three-week versus four-week going to raise an increased issue of confusion or not?

MODLIN: To the best of my knowledge, the three-week interval was largely arbitrary. Roger, do you have any comment? This was the—go ahead.

GLASS: That was just the interval that was used in the trials—was the interval for which we have the most experience. I think as we further experience with this vaccine, we'll learn more about intervals; we'll learn more about immunization of older children. We'll learn a lot more about this. The one comment I was going to make, John, was on the adverse events, if we look at the hospitalizations as the only adverse or major adverse event to date are costly, there have been over 10,000 children immunized. The difference is in the incidence of hospitalization has not been different in the overall group. If you look at subgroups, the difference is about a half a hospitalization per 1,000 children. So we would need post-marketing surveillance of 50,000 children or more to detect that. One of the reasons we'd begin with the VSD data was exactly that. That represents a 2 percent population and it would represent a nice group in which post-licensure surveillance could indicate adverse effects in a period within twelve months of introduction implementation. I think that there's a structure for that—the concerns that Marie represented.

MODLIN: Mimi?

GLODE: I'm still back to the issue of is it, you know, possible to put in place a mechanism that would involve when we were talking about vaccines, particularly if we—for potentially a universal recommendation, have a provisional recommendation that says "17,000 children have received this. A portion of the children are not U.S. children—outside the U.S. Now we're provisionally recommending it for three million, the birth cohort," but there's built in there then a relook at the system in some fixed period of time that allows you to say "Now one million children have received it and here's the safety data on that." Then the provisional recommendation becomes the firm recommendation based on upscaling which, you know, hopefully the results have been the same low rate of adverse reactions.

MODLIN: I don't think we can ever get away from revisiting anything that we do.

GLODE: Well, I don't think we revisit stuff in a standard fashion.

MODLIN: Yeah. Well, true.

GLODE: And I think we should.

MODLIN: Paul?

GLEZEN: In that respect, maybe it would be useful to have Carolyn Hardegree tell us what the FDA requires for post-marketing surveillance. I mean, I think this is already in place. I don't think we have to do anything to do this. Carolyn, could you comment on that?

HARDEGREE: Well, there is no way that FDA mandates post-marketing surveillance. There is a way that adverse reactions have to be reported, but we do not have a requirement that before someone gets a license, they have to tell us everything they're going to do. Now what we do have is before licensure, we work with the manufacturer on a voluntary basis to talk about the type of post-marketing surveillance that we would like to see, tell them some of the things that we would like. I think that in most instances that there is a very good way of post-marketing.

We will be working with each of the companies that are being—vaccines that are being discussed today and tomorrow about trying to set up this, but we don't put into place something that says "We need to see 100,000 subjects in this way." What we usually do is to work with the manufacturer and ask them to bring us in. Now we may have, for example, with the varicella vaccine, said, "We would like to see something else happening. What can we find out about pregnancy registry? What can you find out about what happens in certain age groups about duration?" So yes, there is a voluntary way, but there is not a legal mandate to hold up license until you have everything in place. The manufacturers may want to comment further on that.

MODLIN: Okay. Peter?

PARADISO: Part of the process of actually all new licensed vaccines was to set up a Phase IV protocol to look at large numbers of kids. Carolyn's right; that I guess that it's not mandated, but it's always been part of the discussion for licensure. We've always agreed to do that and do that. For the *Haemophilus* vaccine, for the tetraimmune vaccine, for the acellular vaccines, those have been done in large HMO settings where we can look at hospitalization usage, emergency room visits and fairly rare adverse events over a several period post-vaccination. That certainly will be done in this case and obviously, will be reported to the FDA and can be reported to this Committed as well.

MODLIN: Dave?

FLEMING: I just wanted to do a process check. Where is it that you will try to get the Committee to at the end of this discussion? A specific question I have has to do with at the last meeting, I think we did have a vote on as to whether or not to proceed further with the universal immunization. Were you thinking about revisiting that, or affirming that or some other alternative?

MODLIN: Well, as I explained in the materials that went out with the statement to the Committee members, I certainly had hoped that we could take a vote on the statement at this meeting. At the moment, what I'm considering doing is planning—is asking the Rotavirus Working Group, perhaps with Marie's input, to develop some language along the lines that she's discussed that we could add to the statement that we could revisit tomorrow morning, and take a vote at that time if members of the Committee are comfortable voting on the statement at this time. I guess that's where I'm a little uncertain. I'd like to get a very quick reading as to whether the voting members of the Committee would be willing to vote on the statement with that language involved—included or potentially with that language included once they've had a chance to see it. Are there those—is there anyone who feels that they could not vote on the statement with some additional language, recognizing that the statement undoubtedly will undergo some continuing changes with respect to editing language, wording, et cetera, et cetera. Barbara?

DEBUONO: Well, I think that the—I think that I'd want the statement to be consistent with the conditions or terms for its use set forth by the FDA one too. That not being the case, I'm a little bit uncomfortable with the language that is used relative to the indications for its use. For example, the age range between six years and one year of age—I want to be convinced that that's consistent with what the FDA is going to say in its approval. I'm, again, a little uncomfortable with not having the benefit of that before signing off on the statement. I will say that having, you know, both spent a fair amount of time on this at the last meeting and intervening it at this meeting, I can't support the permissive recommendation. I really think we either go all the way or nothing. We either go to a universal recommendation or we don't recommend this at all.

My issue is the timing of when we say we want to go forward with a universal recommendation: now, well in advance or maybe it's just—maybe it's imminent, this FDA approval; maybe it's not, but I'd like the approval. I'd like a little bit of a sense of where we're going with pricing. There may be some complexities to the price issue that have to do with things that I don't know anything about, but my view is that we're either going to go all the way with this recommendation and have a universal one or not. The timing of the statement to me is—I'm a little confused about, I'm concerned about moving forward on saying, "Yeah, I embrace this statement" without knowing the parameters that might be

set forth by the FDA. So to summarize, if we could somehow caveat any approval of this statement moving forward that we would incorporate any FDA conditions or terms into this statement so that this would be fully consistent with that perhaps with, again, some of Marie's issues being dealt with, then I could support moving forward with the statement.

MODLIN: Okay.

DEBUONO: But I would urge that we not go permissive and we not go step-wise. We make a universal recommendation and promise like we always have to really take a look subsequently and down the road to see if there are any problems or difficulties that have emerged as a result of our recommendation. I wouldn't really caveat the statement beyond that.

MODLIN: Again, I would point out that there's a long time between the time that we approve a statement and the time that it's published. This wouldn't be the first time where there have been substantive changes made in that time. I can think of a couple of examples in the very brief time that I've been on the Committee. So I don't think any of us sees this as set in stone, but it is an effort to move forward. How do others feel about this?

GUERRA: I would so move that we bring this to a vote.

MODLIN: Would you like to see the language that we are proposing to write prior to voting, and a chance we could vote on this? I was thinking that perhaps we could bring this back to the Committee at 8:00 in the morning where we've made some time to do so. Would that be reasonable?

GUERRA: Oh yeah, it's possible to bring it back tomorrow.

MODLIN: Good. That seems to be the consensus, so that's what we'll do. I'm going to ask the working group to somehow or other see if we can't get together, particularly Chuck Vitek, and Joe and Roger. I'd like Marie's input. I'll help out and we'll see what we can do, and we'll take this up again at 8:00 tomorrow morning. We are running beyond, but it's been an important discussion. I will bring discussion to a close now; we'll have our break. Let's come back at 3:55 on the dot.

I would like to ask the members of the Rotavirus Working Group to stay right here in the auditorium at the conclusion of the meeting today. Some of the group are going to go to work right now. What we'd like to do would be to review some language. Hopefully, it'll take just a few minutes at the conclusion of today's session here. There's been a request that Dr. Glode stay as well, perhaps to participate in that from

some of the other members, as well as Dr. Griffin. Let's move on. The next item on the agenda will be the consolidated resolutions for the VFC Program. The discussion is going to be led by Dr. Livengood. John?

LIVENGOOD: Thank you very much. As you remember we started, I think at the last meeting, with discussing the concept that the Committee proceed with consolidated VFC resolutions. Just as a point I'd like to bring up is that this was much harder to put together—simplified resolutions of everything that has happened in the VFC than I anticipated when we started this. So I assure that complaints and all from states and others as to how complicated the VFC resolutions were were not understated. I wanted to just begin because one is easier than the others and start with that. As part of the VFC Program, I think it was Resolution 294. Oh, you have copies of these on your—so even though they're not very legible, this is more just in case we need to talk about particular points.

There's a Resolution 294-1, which was one of the first ones passed, which just makes an official list of the vaccines that are included in the Vaccines For Children Program. As we started reviewing all these, we realized we had that list. It was still on the books and it didn't include hepatitis A, influenza or pneumococcal vaccine at all in the list of things. So we've rewritten this in something that looks very much like the new format, although it doesn't have all the other pieces in it. I'd like to begin with that one. The format we agreed on is that there would be a little introduction here, a preamble—I almost called it a prelude which is musical—a preamble here that just says what this resolution or each of these resolutions does here. It just says that "the purpose is to update Resolution 294-1 pertaining to the vaccines included in the VFC Program." This resolution makes no change to the previous resolution except—and then there's the one thing here it does here. It adds hepatitis A, varicella, influenza, pneumococcal vaccines to the list of this.

We would anticipate that this resolution would be among the first you reach when you go to the home page and you ask for the VFC resolutions. It would list them all and then would refer you on to specific resolutions that would cover each of these topics in more detail. I guess, you know, the biggest problem with this format is that each time we add another resolution, we would need to amend this. Instead of generally amending them and having people traipse through lots of different resolutions, we would propose each time just to reintroduce it, renumber it and repeal the old one just so that we constantly keep one updated page basically or sets of pages for each vaccine or each new vaccine. So this, for example, if rotavirus were to be added at the October meeting or subsequently, we would also redo this resolution as part of that package as well.

On the bottom, all of them now have at the bottom—since we're proposing not to set a different effective date for any of these consolidated ones since they really don't make substantive changes—but that we have at the bottom, under *Adopted and Effective*, that these would all go into effect preferably on the day they were written. That's in all of the resolutions too, so just to point it out. This doesn't have much else in the format because all we wanted to do with this one was just update the current list of all the vaccines that were included in the VFC Program. I don't know if there are any questions. I notice the copies didn't come out with our lovely shading in it that's at the top, but if we can make that publish on the home page, we'll try to do all the little things that make it a little more user-friendly and attractive to the reader. I guess you read on the Internet; I don't—to the surfer or whoever. Are there comments or questions on this one? Yes, Stan.

GALL: I had written a letter to John pertaining to the comments about pregnancy that were included in these items. The thing you have passed out, there is no comment about varicella virus and use in pregnancy. On hepatitis A and others, you quote comments like there's a theoretical risk not indicated in pregnancy. What's the theoretical risk? If you can't list the theoretical risk, then let's not have that statement in there.

LIVENGOOD: So these are specific comments related to some of the later ones? Okay. Then when we get to those. . .

GALL: I assume we're talking about this package you sent us.

LIVENGOOD: Oh no. I thought we should perhaps do them individually. . .

GALL: Oh, okay.

LIVENGOOD: . . .and then come back because this—so it threw me a little at first, but no, I think that those are the types of comments that I think we ought to have. On the substantive ones, just do this first page.

MODLIN: John, do you want to vote on each of these individually?

LIVENGOOD: I think we probably do need to. . .

MODLIN: Okay.

LIVENGOOD: . . .because they're VFC votes and Kevin told me that. . .

SNIDER: Everyone can vote on the list.

LIVENGOOD: Yeah.

MODLIN: This first one's a quickie. Is there any discussion about the—Chuck?

HELMS: You've arranged them in order of. . .

SNIDER: Can't hear you.

LIVENGOOD: Yeah. What order?

HELMS: You've arranged them in order of acceptance into the program.

LIVENGOOD: I think if you think it would be better for the user to put them. . .

HELMS: Alphabetically.

LIVENGOOD: . . .alphabetically because if somebody's looking at it, they obviously don't care, you know, what year it initially entered, but might want to know—"I only know I'm only looking for hepatitis and how do I come down that list?" I mean, that I think would be reasonable.

MODLIN: John, this would be considered Resolution Number 698—mine is cut off—1?

LIVENGOOD: 1, right. We've tried not to put numbers on them until they're approved just in case they're not.

MODLIN: Can we entertain a motion that this resolution be accepted?

HELMS: So moved.

MODLIN: So moved. Seconded? All in favor? Those opposed? The motion carries unanimously by the seven voting members that are present. I'm sorry.

LIVENGOOD: She needs the names.

MODLIN: There are seven voting members present and all voted in the affirmative: Dr. Helms, Dr. Le, Dr. DeBuono, Dr. Glode, Dr. Guerra, Dr. Fleming and myself.

LIVENGOOD: Let me walk you through the varicella one. The purpose of this resolution, it doesn't include any new information. It just takes the current information from the past three resolutions that the ACIP has passed on VFC. It lays out more here the idea of who's eligible. That was based on the vote that was done last year. It's all susceptible children who are at least twelve months old and were born on or after January 1st, 1983. As you remember at the time, it was 1997 so it was just through fourteen. Now it's everybody through fifteen years of age

since we have fixed the date. There's still one other group of people who are eligible, but it was not changed previously, and that's persons who have contact with persons at high risk for serious complications—the subgroup—children eighteen years and under who are susceptible household contacts of immunocompromised individuals.

As you remember initially, they were included regardless of age in the VFC resolutions. So that's a hang-over piece of a small group of people who are eligible beyond just those born since January 1st, 1983. We go and we mention the recommended schedule. This is something I'd like some input on because each VFC resolution before specifically mentions the age at which it appears in the recommended schedule, but that has led some people then to sit down and ask—that that seems inconsistent to them to the previous thing of all susceptible children. So people have expressed some concern that that seems to have the recommended time and the recommended age. It's the first page. The second page has recommended dosage intervals because for persons thirteen years of age and older, you're required two doses. The minimum interval is four weeks between that.

We had, at one point, thought about including recommended dosages, but we were afraid of outdating these all the time on any dosage thing. So routinely we are placing there that the recommended dosage, which is a required element, but that people are referred to the current package insert to cover dosage rather than specifically from this resolution. Then the statement on catch-up vaccination, which the ACIP approved catch-up varicella vaccine for all susceptible children who are least twelve months old and were born on or after January 1st, 1983 to prevent the transmission of varicella. I guess one question, and then I'll let Tom speak about it, as to whether or not we ought to take catch-up vaccination as a category out and just include that as a second part of the recommended varicella vaccine schedule or what the Committee would think we would do between that.

I'd like giving some added prominence to the actual recommended age at which these are developed, but certainly could see how we could do that with one line by itself followed by the statement on catch-up vaccination in that recommended varicella vaccine schedule piece. I don't know, Tom, if you want to—okay—and that might give a better picture of what your recommendation actually is while still prominently displaying the desire for catch-up in a prominent area as well. I guess I am, now that I'm looking for it, I don't see that varicella vaccine use in pregnancy in this part two, and yet it is one of the contraindications in this statement. So I guess I missed it when we were doing these before.

"*Contraindications and Precautions*—the following conditions are contraindications: hypersensitivity to a component of the vaccine or an anaphylactic reaction to neomycin; altered immune status due to malignant condition, such as blood dyscrasia, leukemias except ALL in remission, lymphoma and other neoplasms affecting the bone marrow or lymphatic system"—that's two insets modifying a malignant condition—"primary or acquired immune deficiency, including acquired immunodeficiency syndrome, AIDS or other clinical manifestations of HIV infection; cellular immunodeficiencies, hypogammaglobulinemia and dysgammaglobulinemia; family history of congenital or hereditary immunodeficiency, unless immune competence of possible vaccine recipient is demonstrated; individuals receiving immunosuppressive therapy"—I guess, you know, you gain some by adding the specific types of immunodeficiencies, but you lose something in the translation as well—"and persons receiving high doses of systemic steroids" as defined there. We ought to—I mean, I think pregnancy is clearly one that we need to add to that list.

MODLIN: Okay.

LIVENGOOD: I thought I remembered. . .

MODLIN: There's two issues that you asked us to talk about. One was including the catch-up vaccination under the routine recommendation, was it not? It seems to make alternate sense to me. Does any, let's just—is there any other discussion about that right at the moment? Does anybody feel differently? Chinh, on that specific issue? Okay.

LIVENGOOD: Okay.

MODLIN: That seems reasonable. The second issue has to do with this long list of contraindications. I think there may be one or two issues. I have one, but Chinh, why don't you go ahead?

LE: This is just a clarification for me, you know. I'm still confused going back to the very first group—eligible groups. The previous VFC vote was for children up to fifteen years of age or through fifteen years or age? What was it?

LIVENGOOD: It was through fourteen years of age at that time because they picked the birthdate of 1/1/83. Now because those kids—now since a year has passed since then, it's expanded. Well, it's the same children. It hasn't really changed other that if you gauge it by ages, it's now through fifteen years of age instead of fourteen years of age.

LE: So eventually, every year we're going to push up to. . .

LIVENGOOD: Well, it'll happen; it's the same kids, you know. The baseline is here and by the year 2000, they'll be out of VFC eligibility after 2000.

LE: So it would be wrong to think of this as all susceptible children who are twelve months of age through eighteen years of age? They're not eligible up to eighteen?

LIVENGOOD: They specifically voted not to include. . .

LE: Not to include eighteen.

LIVENGOOD: . . .the upper age groups. That's the infamous 2-1-1 vote that many of us remember so well that we continue to talk about today, but that's sort of where at least we had some degree of consensus around that age.

LE: You know, the way it reads that "susceptible children born on or after January 1983," if I were to read this document in the year 2003, a twenty-year old would still be eligible for this thing.

LIVENGOOD: No, because VFC ends.

LE: VFC stops at eighteen?

LIVENGOOD: Yeah, at the end of eighteen. I think what we ought to do as we get close to that is just change it to all eligible children, you know—twelve months through eighteen years—at a time where it's not going to be controversial to the Committee. So I guess probably in a couple of years, we'll just request a technical adjustment that won't have any real practical effect. I'm not opposed to, at some point, coming back and proposing to add those last couple of years in, but as you heard the relatively few data before and I'm not aware of any additional data right now that provide justification of that other than the idea of simplicity, which in these resolutions is there, but this one item the ACIP specifically picked. I mean, there were four or five options on the list and this was number B—no, C—out of the five options as best I can remember. I haven't been sort of trying to alter things while doing this consolidation too, although it would make sense to me at some point just to make it straightforward, but I thought so last year too.

MODLIN: Okay. Other—Chinh?

LE: One last one. Does the systemic steroid dosing need to also include the duration for—I think for consistency, it's been like "for greater than two weeks" or something.

LIVENGOOD: Yeah. I could look that up in the MMR and maybe copy it exactly like that because I think it's been a certain number of days to two weeks or longer.

MODLIN: I think it would be reasonable. John, this is an issue not just for VFC, but also for the full statement, and that has to do with the contraindication for children who have HIV infection and AIDS. I think some of you may be aware there is some new information that has looked at the risk of varicella infection in HIV-infected children. It appears to be that the major risk is not of significant morbidity or certainly mortality in that HIV-infected children do tend to have slightly more severe infection with varicella when it occurs, but they— most cases are relatively mild and self-limited. The major morbidity instead appears to be the subsequent development of zoster at a much higher rate than non-HIV-infected children, and furthermore, that risk occurs now.

Two separate studies have been shown to occur when children have their varicella at a time when they are moderately to severely immunosuppressed because of their underlying HIV infection. That, therefore, has led to the consideration that this may actually be a group of children for whom we should consider vaccine as an indication as opposed to a contraindication. I don't think this is the time and the place to discuss that issue, but I think it is an issue that we do need to address sooner rather than later as a Committee.

LIVENGOOD: Yeah. I had a note from Jane, just I think in the past week, making that same point.

MODLIN: Right.

LIVENGOOD: I sort of responded just what you said—is I didn't want to bring it up now.

MODLIN: Right.

LIVENGOOD: But I think she is prepared to discuss that soon.

MODLIN: Good.

LIVENGOOD: We're just not ready at this time.

MODLIN: Okay. How do others feel about the issue here though is really listing —having a complete laundry list of contraindications and precautions in the VFC statement? I think it makes sense to do so, but I don't know how others feel. Georges?

PETER: As you talked, I realized that if you have very specific contraindications and precautions in these VFC votes, then each time you modify the contraindications and precautions, you need another VFC vote.

MODLIN: That's true.

PETER: So could you not reference ACIP guidelines so that you wouldn't have to revisit the resolution each time a contraindication was added or deleted?

LIVENGOOD: Do you have any thoughts?

MALONE: Well, the only problem with that is it's no longer a self-contained document.

MODLIN: Kevin, you need to use the microphone.

MALONE: I think the interest here is in making these self-contained documents so that people don't have to go elsewhere. What you're talking about would require a modification of the ACIP recommendation too. So it would seem simple enough to just change both of them at the same time. The other thing you could do is you could cross-reference the package insert as a more living document. . .

LIVENGOOD: The contraindications.

MALONE: . . .yeah, than you guys want.

MODLIN: Georges, I think as a procedural point, it's fairly easy to modify both at the same time. With the interest in keeping this as a stand-alone statement, maybe the better part of the interest is in being more explicit.

FLEMING: As a point of information, is this new or has it always been there? I forget. Is the addition of the precautions a new feature?

LIVENGOOD: No. It's always been required by the VFC law. Several of them, you will see from samples. If we get to hepatitis A today, that we actually skip the contraindications and precautions before, but it is part of what the law says the VFC resolution ought to have in it.

MODLIN: We do need to move through these fairly quickly. Is there any other pressing discussion about this one? Entertain a motion that we accept the resolution before you? Seconded? Dixie, discussion?

SNIDER: What is your opinion about who should vote on these since this has not changed?

MODLIN: I think. . .

MALONE: [Responded off-microphone]

SNIDER: Okay. That means, if I understand correctly, Clover, Griffin, Chinh Le and Modlin cannot vote, which in effect means I have to ask the *ex officios* to vote.

MODLIN: Rich?

CLOVER: Didn't you second it?

MODLIN: Well, that's a good point.

SNIDER: Yes.

MODLIN: He cannot second it; no.

SNIDER: Someone else would have to move and second it.

MODLIN: It's been seconded by Dr. Guerra. Further discussion? Barbara?

DEBUONO: Yeah. You might want to clarify again what's different. It says the— on the varicella piece of it, what's different?

LIVENGOOD: In my opinion, there's no substantive difference from the previous.

DEBUONO: Oh yeah; right.

LIVENGOOD: It's just taking the three separate resolutions from the different years. . .

DEBUONO: And putting it into one.

LIVENGOOD: . . .and putting it all into one.

MODLIN: Right.

DEBUONO: Okay. I can vote, right?

MODLIN: Yes. Tom?

VERNON: You are moving the recommendation on catch-up to page one?

MODLIN: Yes. That was certainly the consensus.

LIVENGOOD: And to add a clear statement on pregnant use and pregnancy, which is off this.

MODLIN: Add a statement on use in pregnancy as well. Those in favor of the motion including the *ex officios*? Dr. Rabinovich, Mr. Graydon, Dr. Trump, Dr. Helms, Dr. DeBuono, Dr. Glode, Dr. Guerra.

LIVENGOOD: Dr. Evans.

MODLIN: And Dr. Evans, pardon me.

DEBUONO: And Fleming.

MODLIN: And Dr. Fleming.

LIVENGOOD: We got lots of votes.

MODLIN: Those opposed? The resolution carries.

LIVENGOOD: Okay. I want to go on to polio. Just to mention one thing about the—oh, you wanted to say something?

MALONE: I'm sorry to interrupt, but can we just for the record, we need to note who the abstentions are so that Gloria can write it down.

MODLIN: Okay. The abstentions include. . .

LIVENGOOD: Abstentions are different from conflict of interest, right? Conflict of interest cannot vote and abstentions are people who are eligible to vote who don't vote.

MALONE: Abstentions are the result of having a conflict of interest.

LIVENGOOD: Okay.

MODLIN: So they are the same thing.

LIVENGOOD: Right.

MODLIN: So those conflicted and abstaining. . .

LIVENGOOD: Or those abstaining.

MODLIN: . . .would be Le, Hardegree, Clover and Modlin.

LIVENGOOD: Okay.

MODLIN: Let's move on.

LIVENGOOD: It's complicated every time we try to do it. Okay. The next one is polio. This does a couple of things beyond just simplifying it; one of which it changes the dose of the third IPV dose in an all-IPV schedule. If you remember at the time the sequential schedule was introduced, IPV was not licensed in the four-dose series for the third dose or it was licensed at about the time, since I'm not sure which happened first, that we adopted the final schedule. So the ACIP resolution, which was passed subsequently, lists the schedule for an all-IPV schedule to be only two, four, twelve to eighteen months, and four to six years. So this one changes that to make the all-IPV and the all-OPV schedule exactly the same at two, four, six to eighteen months, and four to six years.

We also clarified the eligible groups here because that was unclear to some extent in the previous resolution because everybody is eligible. I think we just went right into the two, four, six to eighteen months—I mean, twelve to eighteen months and four to six years for the sequential schedule. So that's one of the few changes. Those are the two changes there. The eligible group here is all children that are six weeks of age, since we don't recommend OPV or IPV before that age, through eighteen years. No one is—the recommended schedule, we list the sequential schedule first and both the other schedules. This is analogous to what was done in the resolution in 10/96. We list some things about the first dose: may be given as early as six weeks of age; completion of polio vaccination with any of the three options is preferred, however, four doses of any polio vaccine by four to six years is considered equivalent to a complete vaccination series when administered according to their licensed indications.

This is something that has been included because with the attention given to that during the sequential schedule discussions, some people, even though they'd receive several doses of OPV previously, elected to complete their series with IPV subsequently because of their desire to avoid any theoretical risk of that, and because there is that statement in the ACIP statement itself; that four doses, as long as you're within the appropriate intervals of any polio vaccine, is considered a sequential—is considered a complete series. So we didn't want people who'd gotten something different from these four ones; that we prefer that you do one of these four schedules that we've offered. We didn't want people having to take another dose of OPV or IPV just because they hadn't completed them in this order.

The recommended dosage intervals—the recommended minimum interval between doses is eight weeks for both OPV and IPV; however, four weeks is acceptable from an accelerated immunization schedule.

The recommended dosage—refer to the package inserts. Oral polio vaccine, contraindications and precautions—the contraindications are immunodeficiency and altered immunocompetence. I'd like to know whether or not you wanted us to go back to a more exclusive list on that. We generally haven't been. We've been broader with that simply because there is a safe alternative, an effective alternative available. We haven't distinguished between subgroups usually with OPV. Infection with HIV or household contact with HIV, immunodeficient household contact, and persons who've experienced an anaphylactic reaction to a previous dose of OPV, and the precaution to administration of OPV is pregnancy.

RABINOVICH: Have there been cases of anaphylaxis to OPV?

LIVENGOOD: I don't know of any, but we usually list anaphylaxis to a previous dose as a generic contraindication. I'd have to—there are people with reported anaphylaxis in VAERS, but I'm not sure in their multiple—yeah—they're multiple things given at the same time. So it's hard. I have not seen anything ascribed specifically to anaphylaxis to OPV.

MCKINNEY: In your statement, you list "it's proven on theoretical grounds to avoid vaccinating," and then you have both the oral and you have—or inactivated. What are these theoretical grounds? There have been several thousand pregnant women who have been administered OPV without any problem in their babies in five years. I don't—I mean, if there are theoretical grounds, what are they? You may want to say that "if you need it, you need to use inactivated enhanced in the adult" or something like that. I mean, this basically, especially with the inactivated, says "it's prudent to avoid vaccinating pregnant women."

MODLIN: The paradox is here that we actually have more data with OPV than we do with IPV with respect to its use in pregnancy. The data with OPV and pregnancy strongly suggests that it is perfectly safe to use in pregnant women. So that I think if this were to be a data-driven statement, which I think it should be, we should remove the precaution for OPV use. Carolyn, do you have any feeling about that?

HARDEGREE: No. I think that the OPV has been in the previous ACIP for years.

MODLIN: That's the problem; is that whatever we do may possibly wind up being inconsistent with the current statement. I'm embarrassed to say what—Dixie, what does the current polio statement say about OPV in pregnancy? My recollection is that I thought we dealt with that issue since we recently revised the polio statement. Okay. On the other hand, I think there probably are very few data with IPV where the precaution is strictly a theoretical precaution there. Paul?

GLEZEN: Well, there have probably been several million doses of IPV given to pregnant women.

MODLIN: Yeah.

GLEZEN: I think the precaution arose from the possibility of contamination at one stage with the SB-40, but I thought that CDC had done a study also exonerating SB-40 contamination. I think either one can be used safely. I don't think there's any need—and there's certainly been a lot of use of IPV in pregnant women.

MODLIN: Again, it may be we are revisiting polio next time, and it may be that it might be, I would suggest going ahead and moving those from the VFC now. When we revisit the polio statement in October, maybe we can deal with that issue at that time just very quickly. Stan?

PLOTKIN: I have a question on another issue just for clarification. Under contraindications for OPV, you seem to distinguish between patients with SCID or hypogammaglobulinemia and others. Is that because you know of no cases in the second group? Why do you say that there is a substantial increased risk in the first group, but a theoretical risk in the second?

LIVENGOOD: I think we copied this from previous statements, is the vague reason that we had a lot of this. We weren't really updating too much. With the—well, most of our cases, frankly, are in the agammaglobulinemia or the severe combined category. I wish Becky were here because she knows these data a lot better than I do. Some of these others are more theoretical in terms of how we would expect—it would be unusual. You'd see them in an infant, but not necessarily in contacts. That's where we would be sort of moving from possible contact with people with some of these other conditions. It's not a very satisfying answer, I'm afraid. We don't have specific data on risks in all these individual groups.

MODLIN: Yeah. The reality is is that the only risk group that we recognize to be at increased risk for vaccine associated polio are individuals who cannot, do not have adequate B cell function. Again, I think if we were going to be data-driven here, we would acknowledge that in the interest of what Neal was raising earlier. It would be helpful to be more specific. Granted, I think it's a very small issue, as you've pointed out, given the fact that there are alternatives—additional alternative vaccines; not one that we should waste a lot of time on; maybe, again, something that we could, for the purposes of the polio statement, visit in October and probably should. For now, I don't know where I stand. I would suggest leaving out the theoretical patients.

SNIDER: What it currently says, you probably don't want to hear it. "Although no adverse effects of OPV or IPV have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided. However, if a pregnant woman requires immediate protection against poliomyelitis, she may be administered OPV or IPV in accordance with the recommended schedules for adults." So you can have it either way.

MODLIN: That's a little schizophrenic, isn't it? Stan, your point is very well taken. I think this is an issue that we probably will have to address on a vaccine-by-vaccine basis as we take it up just for purely administrative reasons and we will. I appreciate that. Now is the time to bring it up. Okay. Yes?

GUERRA: For practical consideration, the use of "and four to six" or "by four to six" sometimes presents dilemmas in decision-making on the front lines, and also in dealing with algorithm decision-making for registries. Because of in the instance of "by four to six," I mean, that is sort of open-ended for that time.

LIVENGOOD: Yeah. Actually, I think that is a major thing to discuss when we hear more from the algorithms group because that's a perfect example of, you know, the dose is scheduled at four to six years of age because of the theoretical better protection in going into school settings, but yet an algorithm would score four of these things separated by "at least among at any ages" as complete and acceptable. So it's one of the difficulties that, you know, we're having dealing with that whole issue with that group; is that, in fact, it's very hard. This is at least one place where it's clear we would accept almost anything in that series as we've sort of laid out specifically here because we were faced with those issues. Yet, we clearly have a recommended schedule that's different from that. It depends—it would depend on whether you were trying to use your registry or your algorithm for reminder recall because you wouldn't recall people until four or six years. If they came in and got another dose whenever they were looked at and audited, it wouldn't prompt you to recall them or give them another dose. So it's a good example of the difference between the optimal schedule, if you will, and a minimally acceptable schedule, which is actually quite different.

GUERRA: Right. I guess it would also be helpful if maybe when we discuss the individual antigen vaccines that we see what the states are doing because again, as children move across state lines and what have you, it get very confusing.

MODLIN: Okay. John, where are we?

LIVENGOOD: So did you want me to make these changes and then come back with this at the next time or are you comfortable?

MODLIN: We can deal with them now very quickly. I don't think they're too difficult for us to handle even at this hour of the day. The changes being?

LIVENGOOD: To change the contraindication and make a statement there that "only people with B cell dysfunction have been documented to be at risk of that." Do you want to just take out the rest about the, you know, the other grounds or the other indications?

MODLIN: I think that would be my preference? How do others feel? Again, in an effort to move in that direction, we might as well do it now.

LIVENGOOD: Okay, and the precautions in pregnancy.

MODLIN: And also the precautions in pregnancy for both vaccines.

LIVENGOOD: Just remove it?

MODLIN: Just remove them. I don't know whether—do we need, actually need to see that language up on the screen or not before we vote? I don't think so in this case, but can we entertain a motion to accept the revised—Phil Hosbach.

HOSBACH: Just a quick comment. When you said those immunodeficients that you were going to break it down, to make sure that you "at increased risk" and not just at risk.

MODLIN: Thank you.

GUERRA: Can you read that again?

LIVENGOOD: Can I just resend this to you, say, next week some time?

MODLIN: Yes.

LIVENGOOD: And you make sure it's consistent with what you said? The concept will be "only those persons with B cell immune dysfunction have been documented to be at increased risk of that under immunodeficiency and altered immunocompromised." Do you want to follow-up with this statement "however, an alternative exists which could be used if there was any question about the patient's condition"?

MODLIN: It's going to be a non-sequitur if you do that.

LIVENGOOD: Yeah. I would prefer not to because it doesn't really fit the format here.

MODLIN: Right.

LIVENGOOD: Okay.

MODLIN: So we'll postpone a vote on polio.

LIVENGOOD: If you want, and then I can send it to you.

MODLIN: Fine.

LIVENGOOD: Just to get us back on time and because the hepatitis people asked me, they're going to ask the Committee to engage in a process that might have substantial impact on what the eligible groups are for hepatitis A. So in which case, we could be at the point of adopting something now and then coming back four months from now and changing it again. So they'd asked, if it didn't bother the Committee, could they just wait to undertake any consideration of hepatitis A consolidated resolution until the next meeting?

MODLIN: Sure. Thanks. That brings us right back on schedule. I wish it was always as easy. Let's move on to the hepatitis A vaccine portion. The major issue here is whether we should be changing recommendations to encourage routine vaccination in selected areas. The topic will be introduced by Dr. Craig Shapiro.

SHAPIRO: Thank you. In the allotted time that we have, we would like to consider the issue of should ACIP recommendations be revised to encourage routine hepatitis A vaccination in selected areas? I'm going to briefly summarize some of the experience to date of using hepatitis A vaccine to control hepatitis A. Then Mike Crutcher, who's the state epidemiologist in Oklahoma, will speak more specifically about their experience in Oklahoma and some of their plans for the future of expanded recommendations for use of vaccine. Then Beth Bell will follow presenting some of the analysis that we've done of hepatitis A epidemiology nationwide, and sort of present a possible or suggested framework for revised recommendation.

Then in the remaining time, we'd like to open it up for discussion, but also propose that after this meeting, a working group be formed of interested members of the ACIP that talk about revision of the ACIP recommendations for a presentation in September, for a decision and a vote if possible. In addition, we've prepared an economic analysis of possible revised recommendations, but it's not fully complete. We're not going to present that this time, but it will be ready to be presented in the fall meeting. Just by way of introduction—can I have the slides

on—a couple of years ago, the MMWR changed their format on how they present in their weekly tables the notifiable diseases. They grouped in Table 2, the notifiable diseases that were not prevented by vaccination. They grouped in Table 3, those diseases that are preventable by vaccination. Our program in the Hepatitis Branch, unfortunately, has the top two on the list and so every week gets a reminder that a large number of cases that are accounted for by hepatitis A and by hepatitis B, and is a reminder that clearly, we can do a lot more with these diseases that are vaccine preventable.

The hepatitis A vaccine has been licensed since 1995. In looking at the epidemiology at that time in terms of formulating ACIP recommendations, it was convenient to group the communities that experienced community-wide outbreaks of hepatitis A and that accounted for the majority of hepatitis A in the United States into high-rate communities and intermediate rate communities. Some of the characteristics of those communities are shown in this slide. In the high-rate communities, the outbreaks that were occurring in these communities, most of the cases were in children. The outbreaks tended to be periodic—sometimes with quite regular periodicity—large outbreaks every five to seven years. These communities tended to be somewhat small, somewhat geographically isolated. Examples of those types of communities are American Indian reservations, Alaskan Native villages and some religious communities, notably the Hasidic Jewish communities where some of the original vaccine efficacy studies were conducted.

Other types of communities that were experiencing community-wide outbreaks were classified as intermediate rate communities. In these communities, the outbreaks involved both children and also adults. Sometimes, they were periodic, but in other communities, they may just be large single outbreaks. These communities tend to be somewhat more geographically dispersed larger—not actually like an isolated Indian reservation or Alaskan Native village—but perhaps a county or even several counties are grouped together. Some examples of, in the last couple of years, large outbreaks in intermediate communities included outbreaks in St. Louis, Memphis and many counties in the western United States. So using this epidemiology, the ACIP recommendations, which were published in 1996, are summarized on this slide.

The recommendations and the feeling of the ACIP members at the time was that really the best way to control this disease was to make hepatitis A vaccine a routine childhood vaccination, but that there were some technical issues that prevented that even to this date, and that the vaccine isn't licensed for children under two years of age. There's some issues that we have to work out regarding dosing to overcome

some of the effects of maternal antibody. So in the interim, recommendations were targeted. They were targeted to persons who had demonstrated increased risk of infection on the basis of epidemiology, including international travelers, homosexual men, injection drug users and a variety of other groups. In addition, the vaccine was recommended for children living in communities with high rates of infection. It was recommended as a routine childhood vaccination starting at two years of age in those high-rate communities.

For the intermediate rate communities, we weren't entirely sure what the recommendation should be. The language was inserted in there that made it permissive such that targeting vaccination to groups in these communities with the highest rates of disease may have an impact in terms of helping control these intermediate rate community-wide outbreaks. The actual effectiveness of this type of recommendation and implementation of this recommendation was yet to be determined. The way that these recommendations were translated into VFC language was that in the high-rate communities, children should be routinely vaccinated at two years of age or above; and that catch-up vaccination also was a high priority in these communities up to an age group that was determined based upon the epidemiologic data; and that sustained childhood vaccination should occur after initiation of catch-up vaccination and routine childhood vaccination.

In the intermediate rate communities, the actual language that was used for the measles VFC vote in terms of controlling outbreaks, we sort of paraphrased it in that during community-wide outbreaks, state and local health authority should be given flexibility to provide vaccine under the VFC Program provided that those outbreak control measures were consistent with ACIP recommendations in that persons in the highest risk rate groups were being targeted in that some program was implemented concurrent with a vaccination program that was evaluating the vaccination program to see whether it was effective or not. Well, during the last three years since the vaccine has been available, a fair number of communities actually have implemented hepatitis A vaccination programs to either try to control ongoing outbreaks or to prevent future outbreaks.

To just provide some summary data on that, this is an example of a high-rate community. The Rosebud Sioux reservation in South Dakota which, as you can see from a number of cases that have been reported over the last several decades, has been pretty typical high-rate community with periodic outbreaks. If you calculate this as rates during the peak epidemics, the rate is approximately 100 times that in the general U.S. population. Beginning in 1995 and early 1996, there was an increase in the number of cases in this community, which spurred on a catch-up vaccination program. Children less than twelve years of age

were targeted in this community. We actually participated in some CASA reviews of the coverage in that community. With this vaccination program, they're able to achieve about 70 percent coverage of children less than twelve years of age.

What was seen is that very rapidly, based upon the previous epidemiology should've blossomed into a large community-wide outbreak. There really was a cessation of cases. Not shown on this slide, in 1997 and 1998 in this community, there have been no cases of hepatitis A reported. This is an example of actually what's been seen in the Alaska, what's been seen in Indian reservations in the southwest; that in these communities, which have somewhat of a centralized health care delivery and relatively high levels of hepatitis A, vaccine coverage can be achieved; and that these vaccination programs in high-rate communities can be effective at controlling ongoing outbreaks. Most of these communities do have sustained childhood vaccination so that with continued vaccination, future outbreaks can be prevented.

The experience in intermediate rate communities is a little bit more mixed. One example of a vaccination program in an intermediate rate community is one that the CDC has been conducting in collaboration with the California State Health Department and the local health department in Butte County, California, which is a county about the size of about 200,000 people that have actually experienced periodic, large outbreaks of hepatitis A. In early 1996, a vaccination program was initiated where the population that was targeted was two to twelve years of age, which was the group that had the highest rate of reported hepatitis A. That included about approximately 30,000 persons. Vaccine was delivered in a variety of school-based clinics and also through the county health department immunization clinics, and subsequently, through VFC providers in the area and other pediatric providers.

The first dose vaccination coverage—I'm sorry; it was initiated in 1995. The first dose vaccination coverage was relatively modest. Overall, it was about 44 percent. What we've seen in these intermediate rate communities is reaching the preschool age group is very difficult. The two- to five-year old age group is just hard to access them with vaccination even if you have day care type vaccination programs. The coverage was 27 percent and in the school-based programs, it was roughly 50 percent. Looking at the number of cases that were reported, historically, you can see is that again, Butte County experienced some of these periodic outbreaks. The vaccination program was started in early 1995, actually, on the down swing of the outbreak that was occurring at that time. This has been an experience in a variety of communities like this of this size where they've tried to initiate a community-wide or a county-wide vaccination program. The time, and

resources and energy that it takes to mobilize such a vaccination effort, sometimes the outbreak actually passes by and it's been hard to actually start the program in the midst of the outbreak.

In addition, what has been seen in a variety of these type of communities is that the outbreak or the diseases don't go away completely. What you can see, actually in 1996 and 1997, the case count increased compared with in 1995. In fact, the cases that were occurring in 1996 and 1997 are actually in older age groups outside the target age group. These are predominantly outbreaks among adult homeless population and injecting drug users in the county. So that another illustration of this is that the age distribution of rates for 1994 when the bulk of the cases were occurring as shown in green here, and you can see that the highest rates are in the young children and adolescent age group. What happened in 1995 and 1996 is that the peak rates are actually in the older age groups. So the vaccine apparently has been somewhat effective or quite effective in reducing the rates in the target age population, but still hepatitis A being transmitted in the community in older age groups.

So the take home points that we have from the experience in intermediate rate communities are that it's been difficult to achieve high coverage levels; it's at most been a modest effect of controlling an outbreak; and because the language, both for the ACIP recommendations and for the VFC language is sort of a focus on outbreak control, oftentimes having a longer view has been difficult, both from a political point of view and sometimes from an economic point of view to take. So that in most of these areas, sustained vaccination of young children in order to prevent future outbreaks is either not done or it's been very difficult to accomplish. So this is a very brief overview of some of the experience to date over the past couple of years in selected areas in the United States. I then want to turn it over to Mike Crutcher who can talk about what's going on in Oklahoma, which is probably a mixture of both high-rate and intermediate rate communities, and talk about what they've decided as a state of a path to take in terms of hepatitis A vaccination.

CRUTCHER: Well, thank you, Craig. Can everybody hear okay? I'll summarize very quickly, as Craig said, and just let you know that what we've done in Oklahoma is just completing, winding down hopefully, a three-year epidemic of hepatitis A, which has consumed a huge amount of public health resources over that time. What we have just done, our legislature and our Board of Health have just approved a plan to begin this fall mandatory vaccination of children entering kindergarten and seventh grade. I believe we're the first state to do that and so I'll spend the next few minutes explaining to you why we made that decision. In general, our epidemic has been one that has been, again, statewide. It

has not been focal at all. It has spread, as I'll show you, across the state. It's been predominantly white, predominantly twenty- to forty-year old adults and predominantly male. There has been a strong association with drug use in that. So we'll go over some of those numbers and let you see what we've seen in Oklahoma.

Now looking at the last ten years of data in Oklahoma, and what I'll spend the majority of my time talking about that, is that right there, which is our current outbreak. It's also important to realize that, again, every five to ten years in Oklahoma, we've had significant blips—nothing like the current one—but certainly, it's not unusual during this time back in the late 1980s and early 1990s where we had rates of 2,400,000 and 600 cases and year. Prior to that—this doesn't go on—but in the certainly late 1970s, early 1980s, there was another big blip there. So the plan, again, that we're looking at, as Craig had mentioned, is not to control the current outbreaks so much, but long-term control of hepatitis A in the State of Oklahoma.

To look more specifically at what was happening here, our current outbreak began in late 1994 and kind of dwindled along here until about the summer of 1995 when it really took off. Over the course of the last three years, you can see on a monthly basis what is happening; whereas, in an endemic year where endemic rates are normally thirty cases a month of hepatitis A, during our outbreak we were seeing 200 to 300 cases per month in Oklahoma. Unfortunately, I took the job as state epidemiologist in the summer of 1995 and had to weather through several unkind jokes from colleagues about did I understand the purpose of my job was to slow the spread of hepatitis A? What I think I have actually learned from this is that once hepatitis is established in a community, it is extremely difficult to stop. Even with extensive public health resources focused on it, I think any of us here who have dealt with that realize that. Anyway, as the saying goes, that's my story and I'm sticking to it.

Just to show you some of those numbers over the year again, in 1994 when it first started, 419 cases. Now compare that to the five-year average prior to that of about 350 cases a year and the rate—and keep that rate in mind—of about 10 per 100,000, which was the endemic rate in Oklahoma as well as in the United States. You can see what our rates did over the ensuing three years in the number of cases. We were hardest hit in 1996. We had 2,500 cases and rates eight times almost our normal rate. Now I just want to show how this has spread across the state. Initially what we did because insurance companies had said that if their members were in outbreak counties or epidemic counties, that they might possibly cover for the cost of hepatitis A vaccine. So we kind of arbitrarily defined an outbreak county as at least

five cases in that county in the year and a rate of 30 per 100,000 or three times the normal rate.

I really don't know how the insurance thing panned out. I don't think we administered too much vaccine during this time, but we just continued to do this. It shows nicely the spread of the disease across the state. So December 1994, these were the only three counties that achieved an epidemic rate at that time. I'll show you six-month increments as it's moved across the state. By the middle of 1995 and in the highest rates in that first year—and I'll show you some of those rates in a second—were indeed in the far eastern part and the south central part of the state. Six months later in the middle of 1996, that number of counties. By now what we were seeing is that the rates here were dropping off and the rates in these counties were really picking up. The middle of 1996, again, now we're in really the brunt of the epidemic, and indeed, the highest rate counties were in the middle part of the state although still holding on here.

Then a year later at the end of 1996, you see the total number of counties that have achieved this rate of disease. So it has really marched nicely right across the state. A lot of effort went into keeping that from happening. Undoubtedly, we prevented some cases and had some impact, but we certainly could not stop hepatitis A from moving across the state. Then a year later, you can see that indeed by the end of 1997, that we are starting to see a fall back in the disease. Now just to show you some of the rates that we were talking about in the first part, this is 1995. So this is the first year of hepatitis A in Oklahoma. All these counties are the far eastern counties in the state, and the number of cases that they had and then the rates of disease, again, with 10 per 100,000 as the endemic rate. We had some quite high rates here.

What is fortunate, during this time anyway, is that it had not moved into the two large metropolitan areas of the state yet, although Tulsa certainly was starting to see—it's in the eastern part of the state—a significant amount of disease. Oklahoma County had not been hard hit yet, but that would certainly change in the next year. Then in 1996, what we see are now counties in the central part of the state have assumed the brunt of the disease and you see the highest rates. Certainly, some of the eastern counties are still there at Stevens, Garfield, Pontotoc. That's a misprint. It should be 45, not 405. The thing that happened in 1996 also is that it moved into our largest metropolitan area in the state. Oklahoma County where Oklahoma City is located, 518 cases and now it jumped from a rate of ten up to a rate of almost ninety.

In the latter part of the outbreak now, again, we see counties in the central part of the state assuming the largest burden of disease. Oklahoma County continued to hold on in kind of the last vestige of disease in the state now. The age distribution has been very stable throughout the epidemic. One thing that's a little contrary to some of the data that Craig presented was that in previous studies that we've seen, the majority of disease has indeed been in the younger age groups. What we are seeing is the majority of our disease in the twenty- to forty-year old age groups. Indeed, this is also consistent, I think, with what a lot of other people are seeing in their current outbreaks. We'll see as we go through this time, again, this is in the early part of the outbreak in 1995 when it was primarily in the eastern predominantly rural part of the state. However, looking at the latter part of the outbreak, in 1997, I think we see that a bigger proportion of cases now are assumed by children, but still the highest rates of disease are still seen in 20- to 29-year old adults.

In looking more specifically now at Oklahoma County—this is Oklahoma County during 1996, again, during the height of the epidemic there—again, I think a higher proportion of children cases that we were seeing, but still the highest rates seen in young adults. So the age distribution has remained remarkably stable throughout the course of the epidemic, however, with an increase in children as it's moved into urban areas. As I said, it's been predominantly a white— whites have been predominantly affected. Now when we see here, Native Americans make up 8 percent of the population of Oklahoma. So when it was in 1995 in the eastern part of the state, Native Americans made up a higher percentage and had the highest rates of disease, but still predominantly a white disease there, and very small numbers of Hispanics, blacks and other groups.

It's important, I think, for everybody to understand that in Oklahoma, there are no reservations; that Native Americans are predominantly in the eastern part of the state, but they are interspersed in the population there and do not live on specific reservations. Also, it's very difficult to know actually what being Native American in Oklahoma means. There are rolls that persons can get on and be classified as Native American, and can, I think, have a very distant Native American connection there to achieve their status on that roll. By saying that, I'm just saying that there are not the traditional Native American, I think, customs and living standards that you might associate with Native Americans on reservations perhaps. So it's difficult to know exactly what, I think, always Native American in Oklahoma means; other than it means they can get health care through the Native American system in the state. These are self-designated classifications.

Looking at 1997 now, it's moved from eastern rural Oklahoma to more western and also more urban disease. You see, that's still now whites makes up the vast majority of the disease. In Oklahoma County in the cities, Native Americans make up only about 4 percent of the population. So they still have a little higher rate, but still the vast majority of the disease is in the white population. Again, specifically looking now at Oklahoma County, our largest urban area, again, the vast majority of the disease is assumed by whites and very little by other groups. To make a point here primarily is this question. This is something that I think many western states are dealing with now. A routine question that's asked when we do a case investigation is "Do you currently use or know of persons who use drugs or interact with persons who use drugs?" It's kind of a generic, not real specific question, but getting at if there is some form of drug use associated with the case.

In Oklahoma over the course of these three years, 21 percent—and during certain years, it was higher than that—but 21 percent answered yes to that question. I think a lot of people are seeing this phenomenon in their states with their outbreaks. It's felt to possibly contribute to this change in the age distribution that we're seeing; that this 28- to 40-year old group is the more likely drug-using ages there. Now at the outset of this outbreak, we devised a plan as to what we were going to do, I think like many states that were having problems. It was based upon kind of just some traditional public health practices. We instituted active surveillance primarily with all the laboratories around the state so that we could be certain that we were hearing about cases as soon as they occurred; rapidly identified new cases so that we could educate them and provide IG for close contacts, which is the recommended procedure; and then a lot of public health education and campaigns aimed at high-risk groups, trying to get to the drug-using groups about the means of transmission and the importance of hygiene; and then the promotion of and recommendation, again, for the use of hepatitis A in high-risk groups.

I think what we saw, as you can see from the numbers that I've presented, that this had very little impact upon controlling this outbreak. Now again, undoubtedly, we prevented some people from getting hepatitis A, but we certainly did not nip this in the bud by any means. Just to show you a little bit again, I made the point that this has consumed huge amounts of resources. Actually in Oklahoma County over the last two years, it's pretty much just taken over their operations. They're identifying all of their cases, trying to track them down to give them IG to handle all of the problems associated with hepatitis A when it occurs in food handlers and in day care centers—so a huge amount of resources. Just to show you what's happened with the amount of IG that we've been giving, you can see how it's increased over the course

of our outbreak, again, during the height of the outbreak, fell off here as much as anything due to the fact that you can't get IG very readily. I mean, we're certainly still trying to give it to people, but that's another issue I think that we're having to deal with in the states is looking for an alternative to using immune globulin. I don't know what the future of that issue is, but it's certainly becoming very difficult right now.

So to close, again, what we had looked at is a situation where trying to make the decision how to use hepatitis A vaccine to effect, to have any impact upon this outbreak as well as outbreaks in the future, looking at the groups that we are trying to get to. Again, I had no thoughts at all that I could stop this outbreak now after a short period of time without vaccinating half the population of the state and that was not feasible. So our plan is to look to longer-term control of hepatitis A in the State of Oklahoma. The way that we're looking to achieve that is to begin increasing immunity levels of our population by vaccinating children entering school because I truly know of no other way to achieve levels of vaccination, of immunity in a population.

MODLIN: Question and a comment. It's hard to imagine that this problem is isolated to Oklahoma, particularly with the data that you've presented. What do we know about what's happening in adjacent areas, such as Kansas and Arkansas?

CRUTCHER: Right.

MODLIN: Is there any information on that?

CRUTCHER: Well, I know that many other states are having similar problems. We've had a quarterly conference call with Kansas and Missouri over the last several years because they've had very similar problems. Their's has been more focal in the southern parts of their state, but certainly other—and maybe someone else can speak more to those numbers—but many southern states, New Mexico, and Arizona, Utah, certainly California, Oregon, Washington are having somewhat similar problems.

MODLIN: The other question is the—maybe we're getting way ahead here, but maybe it's an issue to consider as we discuss it; that is if you immunize children prior to school entry, do we have enough information to suggest that that is likely to have a significant impact on the problem? I raise that by saying that one of the things we know about the epidemiology of this disease is that asymptomatic infections are very common in very young children, and that they often serve as a reservoir to infecting their 20-, 25- and 30-year old parents who are much more likely to develop illness when they become infected. Would you be missing that link by simply immunizing children just prior to starting

school or whether or not we shouldn't—there isn't enough information to suggest that perhaps an alternative strategy might be more effective. Just something—I'm raising the issue now. Obviously, you've thought about it, and I guess maybe I've raised it for other members of the Committee as well. Pierce? I'm sorry. Before we go too far, are there additional presentations to be made?

CRUTCHER: Yeah.

MODLIN: Okay. Let's do that, Pierce. Then we'll move on; I'm sorry.

BELL: What I'm going to do now is sort of go back to the bigger picture of hepatitis A epidemiology nationwide, present you with some features of hepatitis A epidemiology that we think are relevant to hepatitis A vaccination strategies and make some suggestions about directions in which we might move with hepatitis A vaccination recommendations. Then I think there'll be an opportunity to address some of the issues that people have raised. To summarize some of the issues with implementation of the current ACIP recommendations in intermediate rate communities, what you've heard is that there've been some problems with this outbreak control strategy, which really was the focus of the recommendations for hepatitis A vaccine use in intermediate rate communities.

These programs have been difficult to implement. They've had an unclear effect on the course of the outbreak. Although originally there was concern that because most communities experience periodic outbreaks, that there'd be sustained vaccination of young children ongoing, this has rarely been a component of the vaccination programs in intermediate rate communities as opposed to the high-rate communities. Because of some of these difficulties that have been identified with this outbreak control strategy, few communities relative to the number of intermediate rate communities experiencing outbreaks have really initiated programs. So our general sense is that continued implementation of the current recommendations is unlikely to substantially reduce overall hepatitis A rates either in a short-term but also, and perhaps more importantly, over the long-term.

So what we need is a hepatitis A vaccination strategy that's going to result in a reduction in incidence over the long-term. In order to do that, specifically with respect to intermediate rate communities which represent the majority of the population in the country, we need vaccination strategies which result in better uptake so that the recommendations are implemented more widely, and also in sustained programs that result in ongoing vaccination. Specifically for hepatitis A, there is a concern about the feasibility of implementation because as you've heard, the vaccine is not licensed for children younger than two

and so we can't just stick it in with all the other infant vaccines. So what we decided to do was to examine the features of hepatitis A epidemiology nationwide and see what implications this epidemiology might have with respect to these vaccination strategies.

This is overall hepatitis A incidence rates in the United States for the period of 1980 to 1996. I show this just to make a couple of points. One being that the overall national rate generally runs between about 9 and 14 per 100,000 population, and that there was this large peak that occurred in the late 1980s which, by the way, shares some features with the current outbreaks that are occurring. Now our previous analyses of hepatitis epidemiology and the recommendations have focused on communities. Actually in some circumstances, in many cases have focused on targeted areas within communities. What we decided to do was to examine what the epidemiology of hepatitis A is on a statewide basis, and see whether the incidence of hepatitis A in each state clusters around this national average; whether there's a considerable amount of variation among states; and if there is variation among states, whether we could categorize the occurrence of hepatitis A in some way that might be relevant for vaccination strategies.

What we've determined and what I'd like to show you is a categorization which basically indicates that states fall with a fair degree of simplicity into three general categories. This first category includes states that we are calling low rate states. On this slide, which shows hepatitis A incidence for the period of 1996 to 1994, we've plotted the overall occurrence of hepatitis A in the United States in this thick yellow line, and then included a couple of examples of these low rate states. There's a few things that I'd like to point out to you that are features of these states. The first is that incidence is always below the national average, or for the most part, that occasionally we see these peaks which one might call "periodic outbreaks," but that the peaks basically only make it to what is the national average at that time. We don't see times in these low rate states where we see this huge upswing in hepatitis A. These are states with sustained low rates, occasional increases in rates, but the increases are quite modest.

The states that fall into this category include many of the states in the south with the exception Florida, and much of New England and some selected other states around the country. I'll show this to you in another moment. Now there's this category of sort of mid-rate states. Once again on a similar slide with a similar scale on the y-axis, and once again with the U.S. average plotted with this dark yellow line, you can see that in these states, basically hepatitis A incidence follows the national pattern; that in some states there's actually very little periodicity; in other states, that there is some periodicity. The increases that we see and the peak rates really represent only a modest increase

above baseline rates. These are some examples of some of these states: New York, Connecticut, Maryland, Louisiana, a number of other states in the central part of the United States.

Finally, there is this category of high rate states. This is, once again, a similar slide; however, you'll notice that the y-axis is different. The other one, the top of the y-axis was 35 per 100,000 population. These states—and these are examples of these states: New Mexico, Oregon, Washington and Arizona—you see that the lowest rates in these states basically touch the national average. In each one of these states, we see this marked periodicity in hepatitis A incidence. The peak rates reach anywhere from 70 to 90 per 100,000 population. The valleys, as I just mentioned, rarely dip below the national average. So what this suggests is that there is—that the states actually segregate into categories of hepatitis A incidence, and that the patterns are sustained over time, and that we don't see a lot of cross-over from one state which displays this kind of pattern for ten years and then that kind of pattern for the following ten years.

Now we decided to look a little bit more closely at these data. This is a slide of the U.S., obviously, at county level. These different colored boxes do not represent average incidence rate. What these boxes represent are the number of years during the ten-year period of 1984 to 1994 in which the county rate exceeded the national average. We sort of took as a cut-off 10 per 100,000 population. So the counties that are yellow and red are counties where the rates exceeded the national average; for the yellow boxes, six to seven years out of this ten-year period; the red areas, eight to ten years from this ten-year period. What I think becomes quite apparent when you look at this slide is that in some of these high rate states which I just showed you a couple of minutes ago—Washington, Oregon, California, Arizona, New Mexico—we see that the majority of the state is in the red, yellow and green category, suggesting that this pattern of high incidence is not distributed heterogeneously in the counties in these states.

Similarly in some of the areas that I described to you as being low rate states, you see once again that this low incidence is distributed homogeneously for the most part throughout these states, and that we don't see little boxes of red coming up on the middle of these predominantly white states here. In contrast in some of these intermediate areas, we do see some more heterogeneity in terms of the occurrence of hepatitis A at the county level. We can look at that a little bit more closely here on this—this is just a blow-up of the State of Florida. What this indicates is that there do seem to be sort of pockets or patches of the state with rates that are fairly consistently above the national average and other areas of the states where there's actually fairly little disease occurring.

So what we've taken from these analyses is that there is this marked regional variation in hepatitis A incidence. Now we knew that there was a lot of regional variation and heterogeneity in hepatitis A incidence, but what is suggested here is that there are relatively few areas that consistently have these high rates and that these are also the areas that have periodic outbreaks with the highest rates, and that these few areas are actually geographically clustered for the most part. In these areas, a past epidemiologic pattern predicts that hepatitis A is going to continue to occur at high levels and that we don't see this jumping around predominantly of high levels in one part of the country for five years and in another part of the country for another five years. So there is a possibility that a program of ongoing vaccination focused on a relatively small number of states and counties as opposed to communities might have a significant impact on overall hepatitis A rates.

How would we implement such a strategy? Well, the current ACIP recommendations are recognized to be an interim strategy. I would suppose that we could look at this as kind of the next step in an interim strategy, which moves the focus away from communities and towards the states and larger geographic designations as counties and groups of counties that have consistently elevated rates. Because we have seen that these rates are sustained over time, that we would focus on a routine vaccination and that possibly that vaccination of single age cohorts linked to school entry requirements may be the most feasible strategy. Now what we have prepared here are just some ways that recommendations based on this epidemiology might look. There are a couple of slides of these recommendations and a couple of options within these slides in terms of potential recommendations.

So one component—one possible component—would be to say that "states without average annual rates over the last ten years that are at least" and then we could say either "two or three." I'll show you on the next slide the differences depending on how one might say this, but "at least two or three times the national average should consider implementing routine hepatitis A vaccination programs statewide." Examples of such states—and once again, you'll see this on the next slide—are these states that I've listed here. Now this is a slide which ranks states which have had an average annual incidence of at least 20 per 100,000 population in the past ten years by incidence rates. This very faint yellow line here divides the six states where the average rate has been 30 per 100,000 or above. You remember from the last slide that was sort of one of the possible options from the five states where the average rates have been at least 20, but not 30 per 100,000 population.

What the second column here indicates is the cumulative proportion of nationally reported cases accounted for by residents of these states. You'll notice that for the states, the six states with rates of 30 or higher, they accounted for 21 percent of reported cases nationwide during this ten-year period. Only 7 percent of the population resides in these states. Similarly, if we were to extend this down to states with an average rate of 20 per 100,000 or higher, we see that actually these states reported 50 percent of cases during this ten-year period, while accounting for only 22 percent of the overall population. Keeping in mind the issue of possible routine vaccination, I've included on this column the size of the birth cohort. You can see that the size of the birth cohort for these six states is about 260,000 children. This doesn't take into account the proportion that might be VFC eligible; and that the number of the cumulative size of the birth cohort for these eleven states is a little bit less than 950,000 children.

You'll also just notice just as another interesting point that the State of California accounted for approximately 25 percent of reported cases and 12 percent of the population. Now you remember that I showed you on the slide of the county map and of those counties in Florida that there are some states where there is a fair amount of heterogeneity in hepatitis A incidence among counties. So another component of the suggested recommendation might be that in states with lower average annual rates, if they're not implementing a routine vaccination program statewide, to consider routine vaccination in communities by which we might mean counties, or groups of counties or large metropolitan areas where rates have been consistently elevated or periodic outbreaks occur. Examples of states in which there might be some consideration of this sort of strategy would be, for example, the states of Texas of Florida.

Then finally, in terms of suggested recommendations—well, how would we suggest that people implement routine hepatitis A vaccination? Our suggestion at the moment would be to consider vaccination of a single age cohort—choosing a cohort either among two- to five-year olds at school entry or perhaps less as a primary, but perhaps as a secondary single age cohort among adolescents, and that school entry laws or regulations or likely necessary in order to promote high coverage levels. So by way of summary in terms of there's this sequence of thinking on this subject, the current strategy—and once again, I emphasize that we're really focusing on intermediate rate communities here—but the current strategy is unlikely to result in sustained reduction in incidence; that routine vaccination is probably the most effective strategy for achieving a sustained reduction in incidence; that as an interim strategy, we consider routine vaccination of children in areas where rates have been consistently elevated; and that this kind of strategy might significantly reduce hepatitis A incidence over time because of

the geographic clustering that we have observed; and that when a vaccine formulation for infants is available, that we should integrate this into the routine vaccination schedule in all states. That's it. Thanks.

MODLIN: Thank you, Dr. Bell. Terrific amount of information and data presented in a relatively short time. We have about fifteen or twenty minutes for Committee discussion. There are a lot of issues here. We don't have to answer them all, but I think a number of issues were raised for general discussion and we ought to at least get started. Pierce, you were the first.

GARDNER: A couple of things. I'm impressed with the difficulty reported from Oklahoma in comparison with the striking successes in Alaska where people went in and mass immunized instead of going after particular target groups. It seems to me the epidemiology must be different, perhaps complicated by the drug population, which is perhaps the hardest group to get to on a routine thing. So I think the differences in epidemiology may be determined as the success of the strategy. You're going to have to—I'm not sure if the program, I'm not sure if the same epidemiology pertains to all different areas.

BELL: You know, I think that in both settings, really what we were calling—what we were suggesting and what we are suggesting is an accelerated catch-up program. In areas like Alaska, this accelerated catch-up program—one, they're small communities that can include more or less everybody in the targeted age group. Two, you can stop at a certain age group because everybody that's older than that or certainly a large proportion are likely to be immune. In these larger areas, we were—we had been suggesting accelerated catch-up, but accelerated catch-up which of necessity because of logistical concerns because of the size of the entire community is focused and is focused on a fairly small group. We leave this other large—other segment of the population, both other children in the same age group and older people, most of whom are not immune. I think that this is maybe part of the reason why this recommended sort of accelerated catch-up program has met with some kind of mixed success in these larger communities.

GARDNER: Two quick technical questions. One is do we have any more information about post-exposure immunization, whether that's going to be effective? Secondly, the data we were presented earlier showed very good antibody levels after a single dose. Could we make life easier for ourselves by getting additional data as to whether a single dose will be, offer some—in fact, here we're trying to basically get someone some—we'll try to modify the disease in the individual and lessen the transmission. I think we need to look harder at what happens after a single dose. Do you achieve those goals? Does the

second dose, which gives you high level, what's the relative contribution of that?

BELL: We actually are in the process of trying to get a study off the ground through a cooperative agreement with the University of Michigan to study hepatitis A vaccine efficacy post-exposure. It's a difficult study to undertake for a number of reasons that I'm sure you can imagine. We are in the process of trying to do that and get it off the ground. In terms of the second question, all of these data that we've shown and that Craig has shown—for example, in terms of the effectiveness of the vaccine in high-rate communities and the coverage, this is all first dose coverage. So there's little doubt that one dose certainly provides protection relevant to the short-term. There are some data about kind of delayed second dose, particularly in Alaska in a community where they did a demonstration project. They went in and gave one dose and they've now gone back a few years—two or three years later after seeing no disease—and given a second dose to the people that they could find which is not everybody. We don't have a whole lot of other data about long-term, what it means to only have given people one dose. Certainly short-term, one dose is, you know, all we need probably.

MODLIN: Thanks. Chinh?

LE: I found your presentation extremely amazing because it really blew away my preconceived idea about hepatitis A, you know. I always thought hepatitis A was in contrary to rotavirus, which is kind of more democratic. Hepatitis A really, really follows the pattern of a third world. When you look at the disease distribution, you know, California and Oregon being relatively rich states compared to Alabama and so on, a lower rate. I guess my naive question would be are the states reporting? Are they doing the right job? I mean, are they equally as good reporting in one state versus all the requirements of reporting by exactly the same as other states? Is there a bias in reporting?

BELL: Certainly it's given—I mean, it's always hard to say that reporting is exactly equivalent. I think that first of all, hepatitis A is required by law to be reported in all states. I think, in fact, one of the most relevant pieces of data to the issue that you raised comes from the sentinel county study of viral hepatitis, which has actually sort of been an ongoing active surveillance in counties in the United States over a very long period of time. In two of these counties—where one of them is Jefferson County, Alabama; another is Pinellas County, Florida, which is in that northern part of Florida; and then Denver, Colorado; and Pierce County, Washington—we see the same unequal distribution of hepatitis A incidence in those sentinel counties that we see in the country. So for example, there's very, very little hepatitis A that occurs

in the county in Alabama or that county in northern Florida, which suggests to us that these differences that we see are in fact real differences.

MODLIN: Alright. Geoff?

EVANS: I have a question and a comment. I was curious—that's okay; I won't take it personally—I was curious, the states that you mentioned in your slide that are now using it routinely, I guess that's just for selected age groups? I'm wondering if there's been any resistance to that, making it a mandated—I assume that there's mandates behind it or is it just practice?

BELL: There are no states that are currently statewide using vaccine routinely. The State of Oklahoma will be the first state to do that. There are—the vaccine is being used routinely in many Native American communities. In Alaska, it is available routinely. Actually, in Maricopa County in Arizona, they're in the process of implementing a rule which will require it for day care entry so that there are some places where this is beginning to be undertaken; that is a more routine vaccination program with some requirements behind it. It hasn't been implemented anywhere yet to date.

EVANS: Alright. Well, my comment would be this. A year or so ago, Memphis —the City of Memphis—the health officer there began to mandate it or require it for certain high schools in the area. That created a little bit of a backlash. I know the National Immunization Program received phone calls; our program did. One of the complaints, one of the issues was that "you are mandating this vaccine and yet you're not providing liability protection. You're not providing it or you're not providing any compensation for those that may get injured in the process." Now as I pointed out this morning, what drives vaccine into our program is CDC designating it for routine administration in children. Currently, hepatitis A does not have that designation. So states are going to begin to go to this kind of a practice—Oklahoma being the first one apparently. This is going to become an issue and that folds into what you're doing today.

MODLIN: There are lots of issues. Georges?

PETER: Several comments. First, I'm sure that you've given some thought as to what the explanation for the geographical clustering could be. It certainly is striking in the fact in some of the West Coast. Chinh's comment was very appropriate. I just wondered if David Fleming was doing a much better job in Oregon than Barbara DeBuono in New York, but knowing them both, I doubt that's the case. The second comment relates to one that people have begun to address, and that is implementation. Are you, you know—it's one component to make the

recommendation. The second is if you want to be effective, you're going to have to have some means of enforcing.

If indeed you have a two-dose schedule, you can't have a school entry requirement with a first dose. I wondered if you'd give any consideration to the use of schools which has, of course, not been a traditional place for administering vaccines in this country and some opposition exists. I think ultimately, we will have to move to schools for administration. The third is the broader question—the broader offensive against hepatitis A. As it's been said, the idea would be to have a vaccine that could be given in infancy. I wondered where we stood in terms of the likelihood of licensure for vaccine or approval under the age of two and also for the combinations? I don't think we've had an update on that subject in a couple of years.

BELL: Well, the drug companies—representatives of the drug companies might want to comment on that. My general impression is that licensure of the vaccine for children less than two is not on the near horizon. Does anybody want to say anything further about that?

MODLIN: Tom?

VERNON: That's correct.

MODLIN: Okay. Dave Fleming.

PETER: Why is that? Because if we're moving more towards a public health strategy to control this disease, you know, we've learned that the best way to do long-term is through infant immunization. I realize that you're going to have trouble getting into the schedule until you have combination products, and maybe that's perhaps the limiting factor.

VERNON: I should ask David or Barbara—David Neil and/or Barbara Kuter to comment if they would.

NEIL: The major problem is very significant interference by maternal antibody. Of course, in these frequently affected communities, most of the mothers have had HepA and they have extremely high titres of anti-HAV hundreds of thousands of times higher than what you get with immune globulin injection. That has interfered with even doses of HAV vaccine in seropositive infants. Screening of infants, on the other hand, would leave some positive. We would have to wait; it would be expensive and impractical. We have seen in some of these infants the one thing which you don't want with HepA vaccine. Given in the presence of high titres of maternal antibody, we seem to see induction of tolerance without boosting later on as they pass the age of twelve months. So there's a real question whether it will be feasible at any

point to develop such a vaccine that's tolerable and efficacious even in seropositive infants to the extent that it would have to be to recommend universal infant vaccination.

On the other hand, there's also major interference. There's evidence suggesting major interference in combination vaccines when you introduce HepA between HepA and other vaccines. HepA seems to be such a potent antigen, it may perhaps somehow dominate the response of lymphocytes draining the injection site. When you, with certain pilot combinations, there's evidence of interference. So there are several problems on the horizon. If they are to be worked out, will take, I think, considerable time because the ultimate goal originally was to have a combination with HepA in it and also less expensive. It looks as though—due to the age factor, due to the combination interference and due to maternal antibodies—that's quite a ways off.

MODLIN: Sounds like the issue is going to be very similar to measles and that it's going to have to take a close look at just what the appropriate age may be.

PETER: The other issue is. . .

MODLIN: Anyway, we only have time for a couple more comments. Stan Plotkin?

PLOTKIN: Indeed, the issue of vaccination in infancy is complicated although studies are going on. It does raise the question of whether one might consider vaccination in the second year of life or at the end of the first year of life, which would be quite a bit simpler and would not necessarily involve combinations. I did want also, while I have the microphone, to pursue Chinh's comment. For example, in Alabama, do you have serologic data to determine whether, in fact, infection is taking place early in life, and therefore, the apparent difference in the instance of hepatitis is because the clinically recognized cases are not being reported—infection taking place earlier in life? So do you have serologic data to back up the differences?

BELL: Well, I think that that's the best data that we have about that. It comes from the NHANES study. Craig?

SHAPIRO: The NHANES study, we've tested both NHANES II and NHANES III for anti-HIV. You can only look at it in sort of large regional areas like the southwest, southeast, northwest. There doesn't appear to be much difference in the serologic profiles that—the rates are not low in the southeast because everybody's getting infected in childhood. There's still a lot of susceptible so the profiles are not that much different geographically.

MODLIN: Just a couple more. Dave?

FLEMING: Oregon does have a great reporting system, but unfortunately, that's not the explanation for our increased rates of hepatitis A. I had a comment and then a question. The comment is that we do know more than we would wish we knew about hepatitis epidemiology in Oregon. At least most recently, like Oklahoma, it is in the young adult population. There is a much stronger even association with drug use, and particularly methamphetamine drug use in Oregon. The studies that we've done, it does appear to be primarily transmitted among the young adult population. There is little to suggest that there is an unsuspected reservoir in infants or younger children. In fact, epidemiology studies do not show that having a child in your house or diapering kids is even a risk factor for hepatitis A.

So it does appear like it's more of a young adult. In that context, the kind of strategy that we're talking about here would be a long-term solution, and that we would not expect to see immediate short-term gains. It's going to be logistically and politically, therefore, difficult to sell people on this issue of a school entry requirement because, in fact, we don't see much hepatitis A in schools, particularly elementary schools in Oregon. The question I had was related to the combination vaccine; whether the effect that you were talking about is just in infants or in older folks as well does the combination strategy appear to be ineffective? Clearly, the way to make this happen, at least in Oregon, would be to have a combination vaccine that we could have for either entry into school or entry into middle school that could be tagged with another antigen that would require it.

BELL: Does anybody want to comment on the status of the combination vaccines for adolescents and adults?

MODLIN: Dr. Neil?

SADOFF: I'm Jerry Sadoff from Merck. There's no question that we have considered the possibility of an adolescent or pre-adolescent combination, including hepatitis A. The advantage of that would be that it would—because it would be primarily a booster regimen for the other vaccines that would be in the combination, the interference probably wouldn't play a role. Those studies—making those combinations are currently ongoing. So it's a possibility, but then you may need for the hepatitis A component, a later booster of that so that you could give two doses of hepatitis A or you could have an earlier hepatitis A at twelve months of age and then boost into adolescence. So there's a variety of approaches that are ongoing with a number of the companies to try and approach this problem.

BELL: There is a hepatitis A/B combination vaccine licensed in Europe.

LIVENGOOD: And in Canada.

BELL: And Canada, right, but I don't know the details of the status in this country.

LIVENGOOD: A three-dose series. . .

BELL: Right.

LIVENGOOD: . . .years of age.

MODLIN: John, you had your hand up?

LIVENGOOD: Yeah. I just wanted to mention that, you know, there is an A/B combination in Canada. There's a fair amount of data on that.

BELL: In adults.

LIVENGOOD: Well, okay, but then I'm quoting from something I shouldn't quote from.

MODLIN: We're going to have to wrap this up. Fernando, I'm going to give you the last word; I'm sorry, and then we can move on.

GUERRA: Just two quick points. One, I think looking at some of the distribution around the country and also thinking about the considerable increase in hepatitis C, it's going to become a tremendously important public health consideration for the future. Because of the individuals that are at risk for hepatitis C, that given the fact that they're exposed to hepatitis A, I think we'll encounter serious problems in the future in terms of the compromised safety that they find themselves in. The second point is that in reference to, I think, Beth's suggestion for school age cohorts, we have had an ongoing program in San Antonio for the last two years where we have immunized about 18,000 children between the ages of three of seven. In that population of school age children at a time when in our community last year we had 440 somewhat cases of hepatitis A spread throughout the community, within that immediate community where there's children that attend school, there was only one case that we could find within that population that had been protected against hepatitis A.

MODLIN: It certainly sounds like there are merited issues here, many of which we don't completely understand. I think there's no doubt that what needs to happen is to form a small and active working group to begin starting on the issue right away, which is what we'll do. I think that's the best we can do right at the moment. I will speak to John and Dixie about this and we'll do just that, and hopefully have a progress report as soon as

the October meeting. Thank you all very much for, again, presenting a lot of information in a short period of time. The final item on the agenda today will be an update on shortage of immune serum globulin and other immune globulin products. Dr. Bell, will you be introducing the topic or Dr. Golding from FDA? Okay.

BELL: Hello again. As I recall at the last ACIP meeting, there was some questions about immune globulin shortages. So what I'm going to do is just present a brief overview of the shortage of immune globulin for intramuscular administration—IMIG. I'm going to be followed by Dr. Basil Golding of the FDA who's going to give an overview of the important issues with respect to the shortage of immune globulin for intravenous administration—IVIG. It's the same carousel as the hepatitis A stuff, just a little bit further along. Yeah. Okay. I'll go forward. No, it's all the way around. It's the last group of slides on that carousel. That's it; okay.

So as I mentioned, I'm going to be talking about immune globulin for intramuscular administration—IMIG. IMIG, as everyone probably knows, is a sterile preparation of concentrated immunoglobulins, which is made from pooled human plasma and is processed by cold ethanol fractionation. The indications for the use of IMIG include hepatitis A prevention, both pre-exposure and post-exposure; measles prevention in exposed individuals who can't receive measle vaccine; and in individuals with certain immunodeficiency states. Now just to sort of paint the picture, this is sort of the manufacturers and purchasers of IMIG in 1994 before the shortage began. The vast majority of IMIG was manufactured by Armour Pharmaceuticals with a very small amount of IMIG manufactured by the Michigan Department of Health. IMIG was purchased by a wide variety of agencies, including hospitals and pharmacies, physicians, travel clinics, by many, many local health departments, some state health departments and certain parts of the federal government, including the Department of Defense, the Indian Health Service and the State Department for some of their travel-related activities.

Now the shortage of IMIG began in 1994. There are sort of two phases or two components to this shortage. The first shortage began in late 1994 because of increased demand. I'll go over some of the details of this on the next slide, but basically, this increased demand came from the Department of Defense, which made a decision to stockpile IMIG. Exercising its option with Armour Pharmaceuticals, basically purchased or entered into a contract with Armour to purchase their entire year's production. This resulted in large civilian sector back orders. Now this issue of increased demand really only persisted through part of 1995. I'll show you the details of that in a moment. The shortage beginning in 1995 has really been driven by decreased supply. This decreased

supply has to do with both product withdrawals, product discontinuations and cessation of production, and also some interruptions in production.

This is a timeline in which I've put some of the more significant occurrences during this four-year period of the IMIG shortage. What I thought I would do is just to go through some of these occurrences first, and then go back and spend some time talking about what we've tried to do about this shortage. It's unfortunate you can't see the dates down here on the bottom of this slide. As I mentioned, the shortage began because of an increased demand from the Department of Defense. We actually first became aware of this in October in 1994 when we received a telephone call from a state health department was having difficulty locating IMIG for administering to exposed patrons and its infected food handler. When we telephoned Centeon, they told us that, in fact, they had been selling all of their IMIG to the military and, in fact, had back orders from the civilian sector equivalent, as I mentioned, to about one year's production.

Now this shortage from increased demand basically continued through most—in its most acute phase—through early 1995. As you'll remember in March of 1995, hepatitis A vaccine was licensed. After that, the Department of Defense began vaccinating troops. Concomitant with its vaccination of troops, its demand for IMIG decreased. So that this issue of Department of Defense stockpiles and increased demand really stopped being an issue by mid-1996. Really, what we've had to—the major problem over the past three years or so has been the problem with decreased supply. This date here is 12 of 1994, but really to explain the issue of decreased supply, we need to go back to 1992 when the FDA first stated their intention to eventually require that all immune globulin products be manufactured using a viral inactivation step.

In the process of working with the manufacturers towards this goal and of moving towards these viral inactivated products, the FDA, in December of 1994, began testing all of the bulk samples of immune globulin products that were not manufactured using a viral inactivation step—testing them by PCR for hepatitis C virus RNA. So that was in December 1994, and in March—so three months later— the FDA sent a letter to all the manufacturers requiring them to test all of their in-date lots of IMIG with PCR for HCV-RNA. The FDA recommended that those lots that tested positive be quarantined. In fact, what happened—what Armour did in response to this letter from the FDA was to withdraw all of its in-date IMIG lots from distribution. So this had the overall effect of removing all of the supply that might've been sitting on the shelf in state and county health departments left over from back

here, and basically left everyone in the civilian sector completely dependent on month-to-month production.

This continued during 1995 with basically Armour continuing to produce; the DoD requiring less, and therefore, Armour being able to produce some IMIG for the civilian market and Michigan also producing larger IMIG lots than previously. Then consistent with its goals—FDA's goals—in March of 1996, the FDA began testing these bulk samples of immune globulin products using a more sensitive assay, which was termed PCR-2. Once again, consistent with its previous practice, about three months later, it sent a letter to manufacturers requiring them to test in-date lots with a more sensitive assay. Armour, which now has been changed hands and is now called Centeon, responded to the FDA's requirement by not only withdrawing all of its in-date lots, but completely suspending production and stating their intention to produce no further IMIG until they had finished development of their new process, which included a viral inactivation step until that process had been reviewed and approved by the FDA.

This left—since Armour had both withdrawn all of its lots and stopped production—this basically left the country with virtually no IMIG except for what was being made on an ongoing basis by the Michigan Department of Health. Fortuitously at almost precisely the same time, the Massachusetts Department of Health, which had been manufacturing very small quantities of IMIG for in-state use, received approval from the FDA to distribute IMIG nationwide. So we then, since about July or August of 1996, have been left with two manufacturers of IMIG; that being the Massachusetts Department of Health and the Michigan Department of Health. During this period, there have been various increases and decreases in production by these two manufacturers. The bottom line in terms of IMIG supply has been that the supply has been more or less close to completely exhausted by the time the next lot from one of these producers has become available.

Not shown on this slide, this last date is March of this year. It is about this time that Centeon—Armour, now Centeon—got to the final stages of receiving FDA approval for its new IMIG production procedure by the FDA. I should mention that it was not—this long time period was not from any foot dragging on the part of the FDA. Now so what did we do about this shortage? Well, I think that probably the most important thing that we've done to respond to this shortage is to establish a working group. In fact, this working group had its first meeting about one month after that October 1994 telephone call from the state health department. This working group included representatives from all of the manufacturers; from the distributor who began distributing all of the Massachusetts and Michigan IMIG in 1996; from CSTE, FDA, CDC-

National Vaccine Program, and the Department of Defense when the Department of Defense was an important player.

This working group has been very important in terms of establishing consensus and facilitating communication. In attempting to respond to this shortage, we have established—done a number of things, always more or less in the context of this working group. We've established a distribution scheme to maximize the public health impact from the amount of IMIG that was available and received. All of the manufacturers and the distributors agreed voluntarily to abide by the cities' distribution schemes. We have been able to facilitate communication. This has been important—both among the manufacturers, between the manufacturer and the Department of Defense, allowing the Department of Defense to—they were able to Centeon, "Okay, you know, we won't buy this lot. For the next month, you can sell it to the civilian sector." Facilitated communication with the states and counties to keep them up to date with what the circumstances were, how to obtain IMIG and what they could expect, and also facilitated communication with the manufacturers and the FDA.

The FDA has really managed to streamline the approval process after all of the necessary steps have been taken for IMIG so that really once everything has been done, the FDA has now managed to get these things approved within a matter of hours, which has been extremely helpful. CDC has also been involved in the provision of technical assistance, particularly with states and counties in terms of evaluating appropriate indications for IMIG use. The working group has been certainly encouraging production whenever possible—both in terms of increasing the production of the existing producers, and also encouraging companies that hold licenses to produce IMIG to do so. We have been involved with monitoring of supply and identifying circumstances in which severe shortages might, in fact, worsen and letting people know about that in developing contingency plans. We've also been involved in responding to emergencies and identifying large quantities of IMIG when necessary.

Now what has been the impact of the IMIG shortage? Other than driving many of us completely out of our minds, in terms of hepatitis A pre-exposure prophylaxis, I think that it's fair to say that it's been very difficult for travel clinics and others administering hepatitis A pre-exposure prophylaxis to access IMIG. We have modified a suggested distribution scheme over time depending on the availability of IMIG, but for most intents and purposes—for the most part—have been difficult to obtain IMIG for this purpose. We've been actively involved in encouraging hepatitis A vaccine use for pre-exposure prophylaxis. For post-exposure prophylaxis, there've been enormous logistical difficulties. I certainly don't mean to minimize how difficult this has been

for county health departments, state health departments, practicing physicians and many individuals.

We have, given the circumstances, we at CDC have been able to identify IMIG for every circumstance of which we were made aware. So there was never a circumstance during the course of this outbreak in which we heard about somebody that needed 5,000 doses of IMIG or whatever where we were not able to locate it. I think that there are likely to have been circumstances in which we were not aware of shortages of IMIG or inability to locate IMIG, and other circumstance in which people just said, "Well, we can't get it." So I think that it's likely true that IMIG was not offered in some circumstances in post-exposure prophylaxis for which it would've been indicated. We don't have any data to suggest to date that this resulted in any disease, but certainly, it is not something that should occur. For persons using IMIG for immune deficiency, they were likely having to order more frequently because they were not able to get large quantities at a single time.

Just a moment to say, "Well, why did this happen?" I mentioned that certainly some of the issues with respect to product withdrawals and stopping of production has to do with moving to products which include a viral inactivation step. I think that there's some other issues regarding why companies didn't jump right in there. I think that there is this issue of a shrinking market of uncertain size because of the use of hepatitis A vaccine; that there is competition with other products for precursor materials. Some of these other products—for example, such as IVIG, which is also in short supply and may be more profitable to produce—that IMIG is basically purchased by small entities. It's a very decentralized system. These small purchasers keep very limited inventory. So it's not something where you can get an economy of size. Then I think that there is an issue which has been very difficult to get a handle on of to what extent IMIG has been used for off-label indication, such as chronic fatigue syndrome.

So this is where we are today. As I mentioned, the current producers are the Massachusetts Public Health Biologic Laboratories and the Michigan, which is now—it's Michigan Department of Health, now Michigan Biologics Products Institute. The companies that hold licenses to produce IMIG include Bayer Corporation. Only within the last month or so, Bayer—who every time I have asked them, which has been numerous times, has not voiced an interest in manufacturing IMIG. They now actually are currently producing one lot. Unfortunately, most of this initial lot will not be suitable for hepatitis A prevention because it's formulated in 10ml vials without a preservative, and therefore, it can't be used multiple times.

Bayer now has stated that they do plan a regular production schedule, although the quantity and how the IG would be distributed has not been determined. Centeon continues to say that they do plan regular production. As I mentioned, they do have an FDA-approved process now at this point. The timing of when they're actually going to get back into the market is uncertain. So in terms of quantity, in 1997, the estimated distribution based on what the single distributor sent out was 275,000 2ml vials, the majority of which went to county and state health departments for hepatitis A post-exposure prophylaxis. About a quarter went to persons with immune deficiency disorders. Based on recent conversations with members of the working group, it appears that for the next six months or so, we can expect a production of about 200,000 2ml vials, which is more than half of the entire year's production for last year.

For 1999 and beyond, I actually think that there are some very optimistic things on the horizon. Massachusetts has recently said that they have the capacity to potentially increase their production from its current 100,000 doses per year—100,000 2ml vials—to 300,000 2ml vials. This is something that they're actively pursuing. Bayer, as I mentioned, is talking about producing lots of IMIG regularly. Centeon, in addition, we would expect to get back into the market. So that's all I was going to say about IMIG. Do you want Dr. Golding to. . .

MODLIN: Actually, why don't we open this up? We have a few minutes left for questions and discussion. I might start with one, which is 25 percent of last year's production was being used. I'm sorry; we have Dr. Golding coming as well. While he's coming, if I could ask if 25 percent of last year's production was being used in patients with immune deficiencies, that seems like an inappropriate use for IMIG. . .

BELL: This has been hard.

MODLIN: . . .unless IVIG is not available.

BELL: Yeah. This has been hard and it's been difficult, particularly from our perspective being the Hepatitis Branch, and that all of these sort of prioritizations have been by consensus. We have had difficulty kind of getting a representative of this population that uses IMIG for immune deficiency. I don't have the best data on exactly who these people are. My impression is that certainly based on telephone calls, for example, from people's Congressmen, that a certain proportion of them are people with immune deficiency accustomed to using IMIG because it's cheaper and they don't want to change. Another proportion are people possibly who, as I say, are physicians who are prescribing IMIG for what we would call off-label uses, such as multiple chemical hypersensitivities and chronic fatigue syndrome.

MODLIN: Okay. Thank you. Sorry, Dr. Golding.

GOLDING: Good afternoon. I welcome the opportunity to come and present to you the FDA perspective on the immune globulin intravenous shortage. Before starting, I'd like to make one or two personal comments. This is the first time I think—I used to live in Portland, Oregon and I moved to the Washington, D.C. area. Living in Washington, D.C. and hearing all the terrible things that happened there, I think this is the first time that I've seen a statistic that shows up Washington, D.C. to be better than Portland, Oregon. The other gratifying thing is I've spent many hours on the phone with Beth Bell at the CDC. She's been a wonderful help in trying to keep us on track in dealing with the IM shortage. For the first time, I'm actually meeting her face-to-face, which is really nice. The next time she calls me up and says there's a hepatitis outbreak in Oklahoma, I'll be able to put her face to the voice. First slide, please.

So this slide, this is the title of the talk—not so much to focus on my own name—but just to remind myself to say that many people at the FDA all up the ladder have been involved with this crisis. Many divisions and offices at the FDA have spent many hours trying to deal with this situation. So my talk is going to broken down into these various issues—first of all, the evidence of a shortage. How did we find out that there is a shortage? The FDA does not routinely monitor supplies. It was only in 1994 that we started to have a law on the books which said that each manufacturer had to supply us data regarding distribution—six monthly data regarding distribution. This is one area in which we may—in light of the situation—we may want to change the way we operate.

So there've been numerous—there were numerous persistent reports of shortages nationwide, which occurred towards the end of 1997. Now earlier, there had been sporadic reports that there were shortages, but there had been these kinds of reports for many plasma derivatives over many years. It was only towards the end of 1997 that the reports became very numerous. In following up these reports, we were told by directors of major clinics, by distributors and by the manufacturers themselves that there was no IG in the inventories, and there were no IG at the distributors, and physicians were having a terrible time trying to find immune globulin intravenous for their patients. What we also found out that there was increased cost. The cost doubled and some cases even tripled. This was also indirect evidence that there was a real shortage operating. Some of the reasons for the shortage—there was increased demand. This was based on some market research that was done by private market researchers that showed that each year over the last five years, there was an increase by at least 10 percent of demand of immune globulin products.

This increased demand for the intravenous form was partly due to the fact that the indications for intravenous immune globulin had been expanded. In other words, the FDA-approved indications had been expanded. So some manufacturers that were only approved for primary immune deficiency now had trials and had approval for other indications—FDA-approved indications, such as Kawasaki's disease and some situations for bone marrow transplant. In addition, there was a new indication for pediatric HIV disease. That was approved in January of 1996. So there were increased approved indications, but there were also increases in off-label use. Now I could spend a whole hour going through the off-label uses, just listing the off-label uses of immune globulin. This is the area where I thought that perhaps some of you may actually help us with this problem.

The problem is that what is important is to prioritize the use, in our view, for those conditions where clinical trials have been done and which have proven efficacy. So there are multiple other conditions in which efficacy hasn't been proven, but immune globulin intravenous is used. What we are trying to encourage is that physician groups will have policy statements so that they will prioritize the use, so that physicians would be educated to use the immune globulin intravenous more propitiously and so to alleviate the shortage. There have been—and there's no question that there have been—some serious compliance issues that we've had to deal with in the last few years. In fact, some of the products that we regulate have been associated with very serious side effects. We've had to heighten our inspection program and go into these companies, do these inspections and demand that they comply with good manufacturing processes.

This has led to slow-downs, and in some cases, to companies actually stopping to produce various plasma derivatives. This, no doubt, has caused—has been in a factor in the causation of the shortage. Another issue is the "for the art of disease" issue. The FDA now requires that any blood donor will fill out a form that will state whether he or she has any family incidence of the disease or has had any treatments which are associated with higher risk of this disease. What has happened in the last few years is that after a first, or second or many donations, it has been found out by the blood collector, and then the manufacturer and then the FDA that these donations have gone into pools which have been used for making large amounts of products and these products have to be withdrawn. In many cases, as is the case with the IGIV shortage, because the product is in shortage which was used very soon after released, so when these withdrawals have occurred for the most part, the product has already been used up.

So there's been little impact from that point of view. There have been a few situations where several lots from a particular company were withdrawn because of this problem. What also happens in the companies that manufacture these products, they often manufacture it and stop at a certain stage, which they call intermediates, which they place on hold and only come back to them at a later date. Some of the intermediates go into the production of a particular lot, but when a lot is then withdrawn because CJD, they then cannot further process the intermediates. So there's also no question in our minds that the CJD issue has been a factor in the causation of the shortage. This is a graph showing the distribution in the United States of immune globulin in kilograms in different years. As you can see, there's an increase from 1995 to 1996, about a 10 percent increase. What should've occurred in 1997 to account for the increase in demand, which is a factor of 10 percent per year, there should've been an increase of 10 percent, but there was actually a decrease of 10 percent.

So according to our calculations, in 1997, there was actually a 20 percent shortfall in distribution of immune globulin intravenous. When we try and calculate the shortfall and what contributed to the shortfall, clearly the major contribution was due to GMPs or good manufacturing practices. In other words, the necessity to bring the fractionation industry into compliance necessitated a shortage; in some cases, shut-downs until they could come into compliance. So that this accounted for a large portion of the shortage during this time. CJD, as I've already mentioned, was another issue. There are issues here which are hard for us to actually document. For example, companies that make IG intravenous in this country can also export to other countries. We don't know and we have no control over how much they export to other countries.

What we are told by some of these manufacturers off the record, that this can account for as much as 25 percent of the production. So clearly, the export to other countries also accounts for the decreased amount of immune globulin intravenous that's available in the United States. Well, what did we do when we became aware of the shortage? Within quite a short period of time, we contacted upper management. In fact, the lead Deputy Commissioner, Michael Friedman, with his deputies and others including David Fiegal from the Office of Blood, contacted the CEOs of all the manufacturers to indicate our concern, but also to try and see if there were ways we could work together with industry to alleviate the shortage. So we wanted to learn from them first-hand what were the causes of the shortage.

We discussed with them, and are continuing to discuss with them, using products that are approved in Europe for marketing in the United States. We have set up hotline numbers that can be used, can be

accessed by physicians or others to obtain intravenous immune globulin for emergency use. It is obviously the FDA's viewpoint that we need to production and distribution, but that is without compromising the safety or efficacy of the products. In our Lot Release Program, we were able to shorten the release period so we would receive the paperwork from the companies. It used to take us about two to three weeks to process this. Now we're turning these around in a much shorter time period. We have expedited review of licensed supplements related to IGIV and also related to the intramuscular preparations. We formulated a "Dear Dr." letter that was sent out to physicians to provide guidance for prioritizing the use of IGIV. We think that more work has to be done in improving the prioritization at the physician level.

We've also increased efforts to monitor the supply. We're now trying to reach a situation where we can get monthly reports of distribution rather than six-monthly reports. In one situation, immune globulin intravenous that had been made with albumin—which was potentially contaminated with CJD from an at-risk donor—was released for emergency use with appropriate labeling. This involved working with the TSC Advisory Committee and the Blood Product Advisory Committee. Well, what is the current situation? Unfortunately, we still have a shortage. Although the number of complaints have decreased dramatically—and for example, we were receiving in November and December thirty to forty calls a day, and now we're receiving about five to six calls a week—but it's very clear that the shortage continues. In speaking to physicians and patients that have difficulty getting the product, it might take six hours for a physician's office to locate some product for a patient.

Many of the underlying causes have not been resolved, particularly regarding compliance issues. The 800 numbers that are in place for emergency purchase, but in some cases product is available only for consumers who enter into contractual obligations with a particular distributor or with the manufacturer. So we are trying to deal with these issues to try and improve the availability of immune globulins. Future directions—the FDA is considering updating the "Dear Dr." letter to include new hotline telephone numbers and central distribution points for emergency IGIV accessibility; for increasing the monitoring of product distribution on a monthly basis and trending the data by modifying current CJD recommendations, particularly by encouraging labeling of products according to CJD risks and probably setting them aside for emergency use only. The FDA continues to meet with plasma fractionators on an ongoing basis to investigate IGIV from new sources, including sources outside the U.S. The shortage problem will be reduced most substantially as manufacturers come into compliance with good manufacturing practices and production is increased. Thank you for your attention.

MODLIN: Dr. Golding, thank you. Are there questions, or comments or advice members of the Committee would like to. . .

GLODE: Is there a shortage of this product in Europe?

GOLDING: We don't have very good information about that, but talking to European manufacturers, several of them that we've spoken to are willing to increase—some of them already have licenses in this country and now are willing to increase the amount that they allocate to the United States. So I don't think the shortage in Europe is as acute as it is in this country. There are also other manufacturers in Europe that do not licensing arrangements with the U.S. that are now trying to work on ways to do clinical trials and have those approved by the FDA.

MODLIN: Thanks. Fernando?

GUERRA: There are enormous numbers of paid donors in this country. It just seems to me that there would be always available a supply to process and what have you. Do you have any sense of whether or not any of the products that are collected here are sent overseas for processing to European countries or to Asia?

GOLDING: Well, my understanding is that there is a plentiful supply of plasma. So there is plasma for centers and paid donors as you point out. There's a large amount of plasma. A lot of that plasma is sent to other countries. Some of it comes back in the form of finished product, but much of it does not. I don't think that's where the problem is. The problem is that the manufacturers, as they are today, do not have the capability of actually dealing with the plasma that is available to them in making these products. So they have plans and equipment that can deal with a certain volume. They aren't able to deal with it and they— it would take a certain amount of time for them to get up to speed to deal with the situation. You're talking about a long period of time— months and years.

MODLIN: Okay. Other questions or comments? I'm not certain the ACIP has a whole lot to offer, other than I think there are a couple of areas. One of which suggested earlier, which is the issue of inappropriate use. It may be something that the group can do a little bit more thinking and discussion about. There may be some areas in which—I'm thinking out loud now—but there may be some areas in which we can help. I'm having a hard time identifying others. Neal?

HALSEY: We brought this up at the Red Book Committee meeting. Carolyn Hardegree shared with us some information that was available at that time. In fact, we discussed it as much as nine months ago about issuing a specific statement. It turns out the problem goes beyond

pediatrics. It's even larger in internal medicine because treating a single patient for a disease if they don't need it uses up plasma—excuse me, IGIV that could be used for many children. So we encouraged Gina Rabinovich who we might ask tomorrow; we encouraged NIH to undertake a consensus panel over the appropriate prioritization. Several of our members noted that it's already happened, and in fact as of several months ago, almost all institutions have set up priorities for the use of IGIV being the immune globulin replacement in Kawasaki's disease as the highest priority.

So there seemed to be a little less pressure for us to do something within the Academy because it would take six months to get any policy statement out anyway. We really felt there was a need to bring together both pediatric and internal medicine groups, and neurology groups together. I don't really believe, since a lot of this is therapeutic and it's not vaccine-related, that it really belongs at ACIP. We thought that NIH might be able to pull together a consensus group. It might strengthen—and we sent a letter encouraging that—it might strengthen it if somebody from CDC did the same thing. Maybe CDC wants to do it if NIH doesn't want to do it, but it seems to me it has to be in one of those two agencies.

SNIDER: I think the reason we put it on the agenda, as you probably will recall in the Charter for this Committee, it indicates that the ACIP is responsible for making recommendations about the most appropriate application of antigens and related agents. It specifically mentions immune globulins for effective communicable disease control. Since these problems we've been having impact on communicable disease control, it was our feeling that it was important to update the Committee, you know, about the issue. We certainly were not implying that the Committee necessarily would itself make recommendations, but it might take other actions as Neal is suggesting to assist in getting some resolution to the problems that have been pointed out here.

MODLIN: Dave?

FLEMING: I almost hesitate to bring this up, but one of the consequences of the shortage has been that the price of the product has increased. I don't know if that's been a consequence, but the reality is that the price has increased. As a consequence of that, it's been increasingly difficult for the state and local level to find the resources to pay for this product in settings where its use is appropriate. One other thing that we should probably at least consider is whether or not immune globulin should be paid for under VFC. Obviously, that's not what. . .

MODLIN: John, would you like to think about it?

FLEMING: It's a real issue and we probably need to address it and decide one way or the other.

SNIDER: I think what might be helpful though in the shorter term is following through on Neal's line of thinking—his discussion—with some kind of recommendation from this group, which doesn't have to be formulated at 6:30 in the evening, but some kind of recommendation from this group which could be aimed at the Public Health Service. I mean, it doesn't have to be aimed to a specific agency; that we, you know, convened a meeting to discuss, you know, of appropriate experts to discuss this issue and try to formulate some effective solutions. It would just be, you know, a helpful boost along the way.

MODLIN: Okay. Additional thoughts or comments about this? Fernando?

GUERRA: I would certainly agree there is some urgency on the local level.

MODLIN: Right.

GUERRA: In post-exposure prophylaxis, there's been a shortage of rabies immune globulin and then obviously, IMIG for post-exposure to hepatitis. I mean, it has been ongoing for a long time. It's very costly to, you know, to spend the time trying to locate sources of it. Sometimes, you're not able to use it effectively.

MODLIN: Okay. Well, the hour is very late. Obviously, most of us are not functioning on all—my suggestion would be to literally think about this overnight and maybe not readdress it publicly tomorrow, but certainly not let the issue drop, and give some thought to it and perhaps make some suggestions as to what we might—which directions this Committee may go tomorrow and what contributions we might make. With that, I'm going to go ahead and adjourn the meeting for this afternoon. Gloria, dinner reservations are for what time?

KOVACH: 7:00.

MODLIN: 7:00. So I would suggest that those who are going to dinner meet in about fifteen or twenty minutes in front of the Emory Inn. We will begin the meeting at 8:00 tomorrow morning. Okay.

[*THE ACIP MEETING ADJOURNED ON JUNE 24, 1998 AT 6:35 P.M.*]

MODLIN: Please take your seats so we can get started. I think we're close to having a quorum. We've got Chinh, Chuck, Marie, myself, and Mimi and Dave, so we're there.

SNIDER: Yeah; one, two, three, four, five, six because there's Chuck.

MODLIN: Yeah.

SNIDER: And seven; there's Rich. So we can go.

MODLIN: Yeah. Right. Good morning. As with yesterday, we have a chocked agenda today. We'd like to get started on a timely basis. The first item of business will be the revisiting of the rotavirus statement with two or three issues that were left over from yesterday. Roger Glass is going to lead off to present the musings of the working group.

GLASS: Good morning everybody. Is everybody awake?

SNIDER: Good morning, Roger.

GLASS: I hope no one saw the Braves last night. They lost to another team from New York, so we have reason to be humble. That shows we're hospitable. As we were working—our working group was working on the recommendations that you all have, if you look on the first page in the upper left hand corner where it says "ACIP Draft, h:", if you work your way over there, you'll find out that this is the nineteenth revision of this recommendation. So we're going to add a few additions based on our discussions yesterday. There were three items that came up in the discussion yesterday or questions that our working group addressed yesterday afternoon. I want to direct your attention first to page 24 at the bottom or at the end of the recommendations. This is the last section which deals with future needs: surveillance, research, education.

We've added a statement based on some of the conversations which is—discussions which is here. We're going to call this section after *Education—Implementation*. In that *Implementation* is the statement, "The ACIP anticipates that individual physicians and health care providers may require time to incorporate this new vaccine into practice. Therefore, full implementation of this recommendation will not be achieved immediately. During this period of implementation, post-marketing surveillance to further delineate vaccine benefits and risks will be conducted." That addresses the discussion of whether—about 20,000 children who receive vaccine, whether we know enough about adverse events and whether we know how this will work as we move to hundreds of thousands or millions of children—millions of doses.

MODLIN: Any thoughts, discussion, questions from any members and others? Yes, you bet.

SNIDER: John, let me just make one statement. . .

MODLIN: Sure.

SNIDER: . . .to make explicit what I thought was implicit and everybody understood, and that is that in any vaccine, any new vaccine recommendation, particularly if between the time the ACIP makes a recommendation and new information becomes available—whether that's related to the side effects, or costs or whatever—and the recommendation is in the pipeline, then the program, CDC would be in touch with ACIP and be wanting to discuss whether the recommendation should go forward as is. So, you know, I think a lot of discussion that people had around some of the things will be taken care of as part of the normal process. Obviously, there's some information we won't get until there is licensure, and recommendations for use and some experience with it. I just wanted to make that explicit because I think some of the conversation perhaps suggested that there was no opportunity for change after a vote today and that's not. . .

MODLIN: Right.

SNIDER: . . .you know, that's not the case.

MODLIN: Right.

SNIDER: It would be unusual, but if we did have information indicating a need for a revisitation of the issue, we would not be shy about doing that.

MODLIN: I think we all recognize that that's the case. This is simply putting in writing to people who are reading the statement, state exactly the same thing.

SNIDER: I just want to get that in the record.

MODLIN: Marie?

GRIFFIN: I think maybe when you present the other change also—I mean, I think for this vaccine where there's low mortality and low long-term side effects, I think post-marketing surveillance is maybe more important than with other vaccines. So I think CDC also, as well as the manufacturer, needs to have a role in that because CDC is the one who's making the recommendation that all children get immunized. If there is some problem with the vaccine, it's going to very quickly alter the risk benefit ratio. So I think we need to emphasize that post-

marketing surveillance really becomes more important in this era where we're dealing with vaccines that address disease of lower mortality or lower long-term side effects. So I think the several additions were made to emphasize that point and that some people may feel less comfortable using the vaccine right away. They may want to wait for a year or two. I think this also acknowledges that there will be—there may be a slow uptake and that's okay.

GLASS: That concern is in the next set of changes I'm going to present.

MODLIN: Alright. Why don't we see if there are more comments? Georges?

PETER: We may include in the subsequent section, one problem that we're facing is the vaccine is likely to be used in terms of methods that the child receives. So one of the problems would be resources. Would you want to add a section in essence saying that "may require time and resources to incorporate the new vaccine into practice"? In other words, to accommodate the physician who feels compelled to give the vaccine, but realizes that if he does so, he pays out of his own pocket. That would at least allow him the time of period until it's incorporated. It may not be the appropriate section, but I think everyone agrees that we want to prevent rotavirus disease. The concern really is cost. We want this vaccine covered by not only VFC, but by insurance plans. Some statement to that effect, I think, would be very helpful in the gradual integration of this into practice.

MODLIN: There seems to be agreement. Are there any members of the Committee who are uncomfortable with this language? Okay. Let's move on.

GLASS: The second area, let me direct you to page 23. *Reporting Adverse Events*—we had two versions that came out of our committee. Version A, to be added after adverse events. "The recommendation for routine rotavirus immunization is made in view of the high morbidity associated with rotavirus and the favorable cost effectiveness of immunization. In approximately 20,000 children immunized to date, the vaccine has been found to be generally safe and well tolerated. As with any new vaccine, rare adverse events might be identified when many more children are immunized. Post-licensure surveillance will be instituted to identify such rare events and inform physicians promptly if some data become available." Version 2 is basically the same. It says "The recommendation"—or the difference here, I guess we should highlight—"is post-marketing surveillance and prompt detection of serious rare adverse events is especially important for vaccines used in population in which rates of disease-associated mortality and long-term sequelae are low. So it's the same as the first with that additional sentence.

MODLIN: Rich?

CLOVER: The statement about post-licensure surveillance, what is that formally? I mean, I did not hear yesterday a discussion of exactly how that will be accomplished. Is that via the normal VAERS reporting mechanism or is a company going to do something above and beyond?

MODLIN: Peter, can you respond?

PARADISO: We will be doing formal post-marketing surveillance. This is not—I presume that there'll be the normal CDC routes as well, but we will be doing post-marketing surveillance studies for the FDA.

MODLIN: Chinh?

LE: Yes. This. . .

SNIDER: Rich's question raises a more general issue and that is we had some discussion about it last night at dinner. Right now, our policies and procedures says it's the program's responsibility to develop an implementation plan. For example, with the polio recommendation, the program came back to us at a subsequent meeting and said, you know, "Here is our plan for monitoring implementation of the new recommendation. What kind of education program will be undertaken? What kind of monitoring program, you know, will be in place and so forth?" I guess one of the questions for the future is whether a part of the recommendation should be the implementation plan. Our CDC programs need to know that up front and go ahead and write those things into it, or whether in our policies and procedures, we still want the program to develop the implementation plan, but we get a little bit more specific about what we want included in there. I don't care how we do it, but I do feel that the programs need guidance on what our expectations are of them so that when they bring products in here, you know, they know what they're supposed to bring.

MODLIN: Jose?

CORDERO: I just want to point out in the implementation plan similar to the IPV/OPV sequential schedule, it's really two different sections to it. One is the issue of adverse events and what's being done to enhance the adverse events surveillance. The other is the actual monitoring of the acceptance and what are the factors that go along with accepting the vaccine. I think those actually are two different tracks and the latter is one that we have just—actually, I think that IPV/OPV is the first vaccine recommendation that we have actually done that. We're talking—it seems to me that we may need to do a similar thing with rotavirus.

MODLIN: Rich?

CLOVER: You know, part of this might be addressed by the Subcommittees on Immunization Registries and Algorithms because I think most of those committees have in it—or most of those registries have in them adverse events reporting mechanisms. They're really aggressive at trying to supplement the data that's given to the CDC.

MODLIN: Okay. Are there further comments? We have two versions here. They're in essence the same except for the last sentence. I guess I'd like to hear a little bit of discussion about these and how people feel about one or the other. Mimi?

GLODE: I think, from my point of view, either one is completely acceptable. The second version has its negative point; that it's longer. On the other hand, I think it says to the reader that we realize we're transitioning here from vaccines against meningitis that deal with disease with high rates of mortality and morbidity, and moving into situations where people, you know—as shown sort of by the focus group issue yesterday—are going to say, "Well, I'm going to demand a lot of this vaccine because I'm not so impressed in an individual basis with the mortality or morbidity of the disease." So I think it just acknowledges that we recognize that as well.

MODLIN: Fair enough. Other comments? Chuck?

HELMS: I agree with Mimi except I disagree with her last part. I don't think the phrase really adds that much to it. The fact that you've got post-marketing surveillance argues that you're very concerned about adverse events.

MODLIN: Georges?

PETER: John, I had the same reaction when I read that last sentence. It sounds as if there are many things we don't know about this vaccine. It really is apologetic. I think it's going to delay and be used as an excuse not to give the vaccine. In fact, you know, morbidity— mortality in the United States is low. Long-term sequelae are low in this country. So in a way it indicates that it applies to the entire United States if I read it correct.

MODLIN: Marie?

GRIFFIN: Yeah. I mean, I wrote it so I guess I think that we should keep it. I think mortality and long-term sequelae from rotavirus in the United States are low; they're not in all countries. So it talks about rotavirus disease in this country. From other vaccine preventable diseases, long-term sequelae and mortality aren't without the vaccine. So this is saying

"rotavirus in the United States causes lots of morbidity." We say that in the first sentence. On the other hand, it doesn't cause a lot of mortality or long-term sequelae. So without the vaccine, we don't have children dying or suffering long-term consequences. So I think it is—we are entering into a new era where we're recommending universal immunizations or diseases, such as rotavirus, where we don't have a lot of deaths and long-term sequelae. So I guess it's just a difference about whether we have to say that or not; whether it's already clear.

MODLIN: Dave?

FLEMING: Just very quickly, I could live with either. Given the information we got yesterday about the focus groups and the potential need to, in essence, market the statement a little bit, I would favor the longer version that acknowledges that we realize there are potential problems with acceptance. It acknowledges it a little bit more clearly to our audience, but either statement would be fine for me.

MODLIN: Fine. Further discussion? Paul.

GLEZEN: Marie, there's something that bothers me about your argument. Rotavirus diarrhea is not a fatal disease in this country because we have a lot of clinicians who are able to recognize dehydration. The infection itself is a life threatening infection. We know that from what happens in a lot of countries. So I don't—I think you're sort of minimizing or trivializing the disease. I think it's a very serious disease, but it puts a very heavy burden on our health care system. If you see what happens to a baby that comes in dehydrated to the emergency room and have to be rehydrated immediately, and then they have to be tested several times to see if they can tolerate oral fluids and if they can't, then they're put in the hospital. It happens very frequently. So it's—right now, it's a burden on our health care system. It's an epidemic disease which puts a burden which is not constant. So it complicates staffing of clinics and clogs up our emergency rooms, fills the hospitals and everything else. So I think that—I don't want, I don't think the disease should be trivialized. I think we need to look at it from that aspect.

MODLIN: Okay. Fernando?

GUERRA: Yeah. I agree with that. I guess I have some problems with, you know—the more complex you make the statement and the more opportunity for raising questions or red flags, I think it certainly serves to discourage clinicians, health care providers from using it. I think in this instance, it sort of begs the question "Why are they putting that in in this particular segment and not in any number of the others that they have prepared in the past?"

MODLIN: Right. One needs to keep in mind that this obviously, this addition is in the context of the entire statement where the point is made very strongly that this is a disease of high morbidity but low mortality at several places prior to the time. So if someone reads the entire statement, it may seem to be a bit of an addition in that respect. One more comment, Tom, and then we need to. . .

VERNON: The concern I have is that it would appear to suggest that there are other vaccines or diseases for which we have less concern about serious and rare adverse events. Certanly, if we had a great meningococcal vaccine, which does have—a disease which does have disease-associated mortality and long-term sequelae, that we would be less concerned about serious adverse events and post-marketing surveillance for that disease than we are for this one. I just think we are concerned period about serious rare adverse events.

MODLIN: Okay. Let's make a decision on this one right now. I'm going to ask the voting members of the Committee to decide on the long version or the short version here. I think it's the simplest way to do it.

SNIDER: I think it's you and Chinh Le.

MODLIN: I'm not conflicted.

SNIDER: You're not conflicted?

MODLIN: No. Chinh?

LE: I can, yeah.

LIVENGOOD: I don't see why this makes anybody conflicted. I mean, it's just a. . .

MODLIN: And this is not really voting on the statement itself. So I think, Chinh, unless you want to recuse yourself from this particular item.

LE: Well, I'd like to vote. It doesn't make that much difference. If I were to vote, I would vote for the short version.

SNIDER: Well, since Kevin is not here, yeah; I think John's argument is a good one. Let's just have everybody vote on this.

MODLIN: Okay. Everyone then?

SNIDER: Oh, you're here? You see a problem with that?

MALONE: Well, the Wyeth-Lederle product is specifically mentioned in this. So certainly when you go for an approval of the overall statement, I think it would be appropriate for people with conflicts to not vote.

SNIDER: Yes.

MALONE: On this particular issue, I'll leave it at your discretion.

SNIDER: Okay. Our discretion is that everybody can vote.

MODLIN: Everybody can vote, okay. Those in favor of the long version, raise your hands. In favor—Griffin, DeBuono and Fleming. Those in favor of the short version, raise their hands. It's all other voting members of the Committee.

SNIDER: Call them out if you will.

MODLIN: Okay. Dr. Helms, Dr. Clover, Dr. Le, Dr. Modlin, Dr. Guerra, Dr. Glode. Thanks.

GLASS: Our last area of discussion was on the timing of vaccination. I'll direct you to page 5 and also to page 21. On page 5 is the statement on timing of immunization where we say that "the first dose should not be administered after six months of age"—this is middle of the paragraph, page five—"due to an increased rate of febrile reactions after the first dose in older infants; second and third doses should not be administered after twelve months of age." Then on page 21, we include in the precaution section—and this was added to the precaution section in one of our earlier revisions—"if a child fails to receive the vaccine on a recommended schedule at two, four and six months together with other routine immunizations, the child may receive the first dose of vaccine at any time between ages six weeks and six months.

Second and third doses of RRV-TV may be given at any time during the first year of life as long as at least a three-week interval separates doses. Pending further data" and so forth, the insert that we were suggesting since the data from clinical trials and the data from the recommendation from FDA will be consistent, and since we have no data on giving second and third doses to children older than six months of age, we've added in italics "*in the efficacy trials, second and third doses were not administered to children older than 32 weeks of age. Further data are needed*." That clearly states the area of void we have in data despite our recommendation to allow children up to one year of age to receive their second and third doses. That's a discrepancy from the clinical efficacy data and from the FDA—data that will be in the FDA review, but we felt it was consistent with clinical practice.

MODLIN: Barbara, this is included because of concerns that you had. Do you have any. . .

DEBUONO: I think that's fine. I think that reflects the concern I had consistent with, I think, the data that's available for this review as well as the FDA review.

MODLIN: Okay. Mimi?

GLODE: My only revision I'd suggest is, I mean, 32 weeks of age just sort of doesn't translate very well. I'm sure it's scientifically accurate, but I just think people don't think about people as 32 weeks old. I think you'd be better off to use months there. You're talking about somebody who's 8½ months old?

DEBUONO: Yeah.

GLASS: Eight months.

MODLIN: Further comments?

GLASS: John, you might want to ask Dr. Hardegree, Carolyn, if that's consistent.

MODLIN: I'm sorry, Carolyn.

HARDEGREE: The only comment I'll make is that it at least states what the data is.

MODLIN: Okay. I see everyone nodding, so I assume that there is general approval of this statement or this addition. Is there anyone who is uncomfortable with it? Yes, Bill.

SCHAFFNER: I'd just like to ask the pediatricians do you think that statment will dissuade people from giving the first dose? In other words, do you need to say one dose is better than none?

MODLIN: John?

LIVENGOOD: The language actually mentions this. In the 1995 National Immunization Survey, 96 percent of children started their immunizations by three months of age. I think when you're at three months, you're not anticipating running later than eight months completing a series. So I don't see there's a real decision point for the first dose. Now what happens as kids get later as they go along? I don't think this would particularly dissuade people from initiating the series.

SCHAFFNER: Okay. Thank you.

MODLIN: Okay. I think there's general agreement, Roger, that this is a positive addition to the statement. Okay. If that's the case—Chinh?

LE: Roger, before you leave the podium, can I ask you a question? Yesterday, you mentioned that the G9 serotype may be emerging. Would you expect the vaccine to be less effective in the real world now? Secondly, I guess the technology does allow recombinant vaccine to incorporate more genometry. Is that something that can be done if the G9s seem to be more prevalent?

GLASS: Two things, Chinh. One is that I know that both the vaccine manufacture in the U.S. are considering G9 reassortants. So they're already anticipating that they might have to do something. On the other hand, the early monovalent vaccine trials with bovine vaccine were very effective against human serotypes. So there is a high level of cross-protection. We don't understand what all the epitopes are and we won't really know if the tetravalent protects against G9 until we actually do a trial in a city like Indianapolis, which may have G9 at the time. It's very hard to anticipate. Also, I think the importance of rotavirus surveillance, laboratory surveillance of strains will be imperative. When we started this study, I was very unenthusiastic because we had only found monotonous serotypes 1 to 4 in the U.S. It was only through the persistence of Jon Gentsch and Madhu Ramachandran in the laboratory that that they found this unusual event. So if anything, it's underscored the need to maintain that routine activity in perhaps on a broader scale. We'll only know after the data is in.

MODLIN: Further discussion? If that's the case, I'd certainly be willing to entertain a motion that we accept the rotavirus statement.

GUERRA: So moved.

MODLIN: It's been moved by Dr. Guerra, seconded by Dr. Fleming. I understand that in this case, everyone except Dr. Le is eligible to vote. Those in favor of the motion? Those in favor—Dr. Helms, Dr. Clover, Dr. Griffin, Dr. Modlin, Dr. Guerra, Dr. Glode, Dr. DeBuono and Dr. Fleming.

SNIDER: And Dr. Le abstains.

MODLIN: And Dr. Le abstains. Thank you.

HALSEY: John?

MODLIN: Neal.

HALSEY: Roger, you didn't mention a point that was mentioned in the working group, which I hope that everybody accepts now that this vote has been

taken. There are at least a half a dozen other concerns over specific language that I felt was somewhat problematic, but it's not a huge difference in any of the policy. Now that you've voted, this is not the final language, I would hope, because I hope that those issues are being corrected. You didn't mention this this morning, Roger, and that that is the intent of the working group is that there would be some addressing of those issues.

MODLIN: I think we mentioned that yesterday, Neal, when we said that we had decided to take a vote; that we all recognize, as with every statement, there continues to be some—after the statement is approved and continue to work on it. The whole point here, obviously, is to take a vote on the substantive policy.

HALSEY: I just wanted to make sure people didn't carry it away that this is the final language.

MODLIN: Right.

HALSEY: And it may be quoted as such; it's not.

MODLIN: Thanks.

SNIDER: It never is until the MMWR is through with it.

MODLIN: Okay. Let's move on.

GLASS: I think there aren't any changes. If there should be any additional edits, this is draft number nineteen. Perhaps in draft twenty, we'll have edits from everyone. We have a whole pile from Neal already. So thank you very much.

MODLIN: Not just Neal. We're willing to—again, for everyone in the room— we're certainly willing to entertain suggestions on the drafts. So please get those in and get them in within the next three to four weeks, please, if you have suggestions to make.

SNIDER: Also for the record, once these changes are made, and the document is submitted to the MMWR and they do their editorial business, it is our routine practice to distribute that to the ACIP so that if there are any last minute problems that are of concern to the members, that you have an opportunity to bring that to our attention.

MODLIN: Okay. The next item on the agenda is the harmonized recommendations on combination vaccines. Mimi, are you going to be leading the discussion or is Bruce? Okay.

GLODE: Bruce and I are going to co-moderate this section. I must apologize to you that we're only on draft thirteen here, so we're not really quite up to speed with the rotavirus statement. As all of you recall, it was in the fall, I believe, of 1996 really that the recommendation first surfaced to try to put together a combination vaccine statement. A working group was formed and then a meeting was held here in Atlanta in January of 1997. So we will be, this fall, going on two years with this. So we are anxious to bring some closure to this issue if possible. Over this period of time then, one of the issues that's come forward and the format we've worked with really is to develop a statement that will be published jointly—issued jointly and published simultaneously by CDC, AAP and AAFP. So that's the way the statement has been developed and what we're still hoping will happen.

This morning, we're also hopeful that the working group, at least, is going to request that the Advisory Committee approve the current draft statement, again, I think, with the proviso that we're hoping that there will not be substantive changes. If there are, we would then return this to the Committee. There will definitely be additional editorial work done on the statement. We've already had, of course, lots of input from the working group and also from the Committee members with various drafts. There's still a lot of editorial work in terms of attempting to provide—make this statement as concise as possible. So we do anticipate, as noted here, minor stylistic revisions to draft thirteen. We recognize that there is a fair amount of work to be done with the clearance and editing process to try and get this to occur simultaneously. There's going to be some efforts to get the editors together from these three organizations as well. Okay.

So what we thought we might do first is just review for you again the six boldfaced recommendations. At least for the last several drafts, most of the working group have been comfortable with these six boldfaced recommendations. Most of our work has been initially started on developing those, but now has been on the explanatory information that follows these. I thought maybe I'd just quickly review the six major boldfaced recommendations for you. So first is number one, the "***Preference for Combination Vaccines*—In general, the use of licensed combination vaccines is preferred over the separate injection of their equivalent component vaccines.**"

Number two, "***Interchangeability*—In general, vaccines from different manufacturers which protect against the same disease may be administered interchangeably in sequential doses in the immunization series for an individual patient (example, HepA, HepB and Hib). However, until data supporting interchangeability of acellular pertussis vaccines become available, vaccines from the same manufacturers should be used, whenever feasible, for at**

least the first three doses in the pertussis series. Providers who cannot determine which DTaP vaccine was previously administered, or who do not have the same one, should use any of the licensed acellular pertussis products to continue the immunization series."

Number three, "***Vaccine Supply*—Immunization clinics and providers should maintain a supply of vaccines that will protect children from all the diseases specified in the Recommended Childhood Immunization Schedule. This responsibility may be fulfilled by stocking a variety of combination and monovalent vaccine products. However, it is acceptable not to stock all available combination and monovalent vaccines, or multiple brands of each.**"

Number four, "***Extra Dose of Vaccine Antigens*—The use of a combination vaccine containing some antigens not indicated at the time for the patient may be justified when (a) products which contain only the needed antigens are not readily available or would result in extra injections, and (b) the potential benefits to the child outweigh the risk of adverse events associated with the extra antigens. An extra dose of most live virus vaccines and Hib or HepB vaccines has not been found deleterious. Extra doses given earlier than the recommended intervals for certain vaccines, however, such as tetanus toxoid and pneumococcal polysaccharide, may increase the risk of adverse reactions.**"

"***Improving Immunization Records*—Immunization programs should give high priority to improving the convenience and accuracy of transferring vaccine identify information into medical records and immunization registries, as well as the timely availability to providers of the prior immunization history of their patients.**" Then number six was "***Research Priorities*,**" where we talked about information related to carrier proteins to research on alternative delivery systems, transdermal mucosal immunizations, et cetera; the need for more data on interchangeability of vaccines from different manufacturers; the need for more data on additional doses of vaccines and whether there's an increased in adverse reactions; and economic operations research on impact of multiple injections.

So I just wanted to review those six boldfaced recommendations. That's great, Bruce. We essentially had just at least—we're going to open it up for comments on any part of the statement—but we had three question for the Committee from the working group yesterday that we would like your opinion on. The first of those is on page 5 of draft 13, lines 5 through 8, which is in the first section which is under *Preference*

for Combination Vaccines and then under the subsection *Resistance to Multiple Injections*. Okay. In lines 5 through 8 then, the Committee had some disagreement about whether these clauses were helpful to the reader. So let me just read 5 through 8. "This reluctance can lead to deferred vaccination in either additional follow-up visits or missed follow-up resulting in decreased vaccination coverage and likely increased disease burden."

So again, this is discussing a possible consequence of multiple injections and resistance to multiple injections. I guess some members of the Committee felt that maybe, you know, we were kind of overstating things a little bit. I wonder what the Committee thinks about whether or not this is a reasonable argument to leave in or it would be better deleted from the statement—if anybody has any strong feelings?

MODLIN: Fernando?

GUERRA: I think it's overstated. I was going to ask, John, would some of the surveys have revealed in terms of parents' reluctance to the number of injections? I believe that Lance has looked at some of that, hasn't he?

LIVENGOOD: I think he has, but because the age range of the survey is 19 to 35 months, some of the concern is primarily around the IPV/OPV. We're just getting the youngest—those kids who had that are just entering the sampling frame now for National Immunization Survey. I think there is a fair amount of evidence that parents and physicians prefer a lower number of injections. There seems to be a stronger preference on the part of the provider than it is of the parent, but you know, I don't know if you want to talk about some of those things that you have up there on the thing. I think that that's been found pretty consistently across a wide range, but I have heard of—we reported on one study from Northern California Kaiser where they're giving five injections at the first two visits. It's a study that you have to opt into and it's a placebo control study, so I don't know. That's beyond my limit of how many I think I could give. Clearly it's, again, a provider doesn't want to stick a child that much; I'm assuming parents don't either.

MODLIN: Neal?

HALSEY: I'm the one who recommended omission of this because I think the statement is incorrect as worded. It fuels some of the antagonism towards change that we have had to implement in recent years and reluctance to accept the sequential immunization schedule. First, there are no data to show that there's increased disease burden, which it says that there are here. It says "likely increased disease burden." That was hypothesized; that has not been borne out. There also are no data to show that there have been necessarily missed follow-up, decreased vaccination coverage. Just the opposite has happened with

this change. So I think the statement is incorrect and doesn't belong here. It's misleading.

MODLIN: Jose?

WENIGER: Let me just try to respond to what are these references here that not everyone may have reviewed. The reference is Dietz, Wood, Holt and Lieu, and are essentially linking low vaccine coverage to missed opportunities in a variety of cities. The Hutchins one is linking the measles epidemic with missed opportunities. So I think where there is a statement or a conclusion drawn, it was certainly not of evidence quality A, but obviously C. Since you cannot do a random trial, it's to make a—draw a conclusion or an opinion that what the resistance to multiple injections that we've seen from those surveys is a contributing factor to missed opportunities. So I think that is where the leap of logic is made for this to try to justify the preference for combination vaccines.

HALSEY: I just would counter I know all of those studies. Our group participated in one of them and it wasn't fear of injections. It was the providers not providing the opportunities. So it's incorrectly referenced.

MODLIN: It's the logic here. B follows A and C follows B, but C doesn't necessarily follow A.

HALSEY: Correct.

MODLIN: That's the problem that you're getting at?

HALSEY: Yeah.

MODLIN: Okay. Jose?

CORDERO: I think that also we need to look at the context of where we are today with immunizations versus where things were at the time of some of these studies. I've been surprised like looking at all the limited data on the Oklahoma immunization registry for looking specifically at a sequential schedule and what it's done to the coverage in general. It hasn't decreased the coverage overall, which is what you would expect if there is a reluctance to use multiple injections as it would be required with a sequential schedule of IPV. The second thing is that in all the focus groups that were done prior to implementation of the sequential schedule, in every case, every instance when parents were given the option of saying, "Look, I would rather come back and have fewer injections or have four injections and have one visit," overwhelmingly, the response was "I would rather have the four injections." There is really in none of the focus groups any evidence that parents really had

a reluctance to have multiple injections. This has served more—this is what we have for 1996/1997. This is some much older data.

MODLIN: Is there anyone who feels strongly that the language should be retained? It sounds like the consensus is to strike the sentence.

GLODE: Okay. Great. Next is, I think, on page 7. Is that the next one? Right. Under the section on *Interchangeability*, lines 11 through 19. What has happened is that, again, we have talked about interchangeability and then in lines 11 through 19, we gave an example—a relatively complicated example—but an issue that does come up quite frequently and that has been confusing for a long time. The issue deals with interchangeability of *h. influenzae* b conjugate vaccines. It says, "for example, an infant receives at two months of age a first dose of PRP-OMP Hib which requires two primary doses at two and four months, plus a booster at twelve to fifteen months, and at four months of age receives a different Hib vaccine from a manufacturer requiring three primary doses at two, four and six, plus a twelve to fifteen month booster.

In such case, at six months a third dose of any of these Hib or Hib combination vaccines should be given. Regardless of the Hib vaccine type or brand used in a primary series initiated at any age, any licensed Hib conjugate vaccine may be used interchangeably for the booster dose recommended after twelve months of age." So this information is available in the Hib statement. So it's not new information or any new recommendation. The question is is it more helpful or does it lengthen the statement and should it be deleted?

MODLIN: Chuck?

HELMS: Mimi, I think it sort of comes as a brick in the way of the flow of the document. I am in favor of examples like this, but I'm not sure that in this document is the place. Maybe some little pamphlet about helpful examples of this would be the place to put it, but I don't think this is the place.

GUERRA: I would support that as well.

MODLIN: Peter?

PARADISO: May I make a comment on that point? It seems to me that the example that you've picked—and I know you're going to take it out so it doesn't matter—but the example that you've picked is actually one for which there is data. In fact, the data is that if you did get one shot of PRP-OMP, then you need two shots of a different vaccine if you switched vaccines to one of the other two. So the example that's in there is not

one that would cause you to do something different than would be—the evidence would show. It seems to me that the examples that you need are examples where it's not obvious that you need it. Is that right? I mean, where you had two doses and you were fully immunized. You've got two doses of PRP-OMP and the question is now whether to give a third dose of another vaccine because it's not another dose. The way you've described it here it's the way it's supposed to be given based on the evidence.

GLODE: No. It just presents a sort of, you know, complex interchangeability phone call type situation; that's what it presents that comes up fairly often. I don't know whether it belongs in the statement or not.

CLOVER: This is a very frequent question I get—not the one that you had previously alluded to.

GLODE: Sure.

CLOVER: So I think it needs to be in there somewhere. I'm not sure if this is the right location or not, but I think that information would be helpful to the providers.

GLODE: Yeah. So I guess we could think about—we had talked actually at some point in the last eighteen months about—when we were even doing the format of the statement about, you know—whether there should be an appendix that's, you know, common questions asked about combination vaccines or something, or a footnote or some other way of maybe dealing with these issues or, as you mentioned, Chuck, maybe a different pamphlet called *Common Questions Asked About Combination Vaccines* or something. I don't know.

MODLIN: Well, rather than having a different pamphlet, perhaps just referring the reader to the statement—the Hib statement.

GLODE: The Hib statement, right. Yeah.

MODLIN: And to page "X" on the Hib statement specifically, or section such that most of your readers are going to have access. If they have this document, they'll have the other document.

GLODE: Okay. So consensus would be probably to delete this example?

MODLIN: That's the sense I get, yes.

GLODE: The sense I got too, okay. Then the last issue begins on page 11, but there's also something to refer to on page 9. This is under ***Extra Doses of Vaccine Antigens***. In the boldfaced recommendation, as

you recall, we mentioned pneumococcal polysaccharide in the sentence "**Extra doses given earlier than the recommended intervals for certain vaccines, however, such as tetanus toxoid and pneumococcal polysaccharide, may increase the risk of adverse reactions.**" That's in the boldfaced on page 9. Then on page 11, we deal specifically with pneumococcal polysaccharide. Again, there were a number of members of the Committee who felt—some members of the Committee felt that the reference to pneumococcal polysaccharide as an example should not be dealt with in this statement. Other members felt it was appropriate to deal with it, but wanted to shorten this section by deleting lines 24 through 31.

So under pneumococcal polysaccharide, we said "Caution is advised in administering a second dose of pneumococcal polysaccharide vaccine before the recommended interval since prior vaccination. Revaccination of pneumococcal polysaccharide within two years of primary vaccination may increase the frequency and duration of local adverse reactions. Revaccination at intervals of four years or more was not associated with increased local side effects in some studies, but it was in another. Only one revaccination with pneumococcal polysaccharide is recommended after an interval of five years or more from the first vaccination and only for immunocompetent persons greater than or equal to two years of age at highest risk for serious pneumococcal infection, or for those greater than or equal to 65 years who are less than 65 years at the first vaccination. An exception to the five-year interval, however, is made for children with certain underlying conditions who receive pneumococcal polysaccharide at two years of age. They should be revaccinated at five years of age."

MODLIN: Comments? Dave?

FLEMING: I think I was one of the people who suggested this section be deleted. I found it confusing because we're talking about a statement on combination antigens. While I'm not necessarily quibbling the information that's in there, I thought it belonged more appropriately in the pneumococcal statement. I'm concerned that this could lead people to be thinking, "Well, which combination vaccine is it that they're talking about here where I should be concerned about this issue?" So to me, it just seemed to be sort of "true-true" but unrelated to the primary intent of the statement.

MODLIN: Carolyn?

HARDEGREE: Oh, I think that the pneumococcal vaccine is indeed considered a combination vaccine, meaning that it's a combination of numerous serotypes so that that's the context that we have viewed these. In fact, as you move into—I mean, the same would be true for meningococcus

vaccines as well. Rotavirus, OPV, all of these that have more than one group or type have been considered combinations.

GUERRA: It seems to me if that's the case, then somewhere we probably should redefine that then because I certainly would not have picked up on the fact that this would fit into our traditional thinking for combination vaccines as we have tried to use it here. I think it could confuse the clinicians.

WENIGER: If I can—John, can I just provide a little historical background for how this came into the statement? It was not initially in the statement in the first several drafts last year. It was requested, when we got into the difficult subject of extra doses of vaccine antigens, to provide some illustrations of examples when those extra doses might not be wise. So the context of this is not principally because it's a combination vaccine—even though technically it is—but more, "Here's an example in addition to tetanus of why you need to be a little cautious in some cases of not giving extra doses of antigens." That was—it was recommended by someone at one of the full ACIP meetings when we presented this maybe about a year ago; put in something about some adult—generally adult vaccines. Then we put it in, so now we're turning full circle again.

MODLIN: Jose?

CORDERO: I think then we need to do something in the summary on the second page because it says "Combination vaccines"—this is page 1, line 9—"Combination vaccines, which merge vaccines for different diseases into a single product, are difficult to develop." I think that's the only definition I found. Is there another definition that I missed?

WENIGER: That is the only definition we have of combination vaccines.

CORDERO: Okay. So how do we deal with Dr. Hardegree's definition of combination vaccine?

GLODE: It depends on whether you believe that pneumococcal meningitis due to serotype 9 is a different disease than pneumococcal meningitis due to serotype 6. How specific do you want to be about the diseases?

CORDERO: Not that specific.

MODLIN: Right. Neal?

HALSEY: I think maybe we could get around it and say—by just saying "different infectious agents." I was going to say organisms, but I'm not sure a virus is an organism. Let me—I have to think about that a second, but because of DTP, many of the DTaPs are several different antigens for the same organism. OPV, I've considered to be a combination; I think

FDA considers to be a combination and so we have—and then pneumococcus is a combination. So we need to say just if they're different infectious agents or something like that.

MODLIN: Bill?

SCHAFFNER: One would be a little deft in the writing, "although. . .for the purposes of this statement," go into this.

MODLIN: Alright. Carolyn?

WENIGER: I think we've been reluctant to put a glossary in here because unfortunately, our nomenclature for words like "vaccine" and "antigen" is very unhelpful and they're not very precise terms. Sometimes antigen means one thing and sometimes it's used for another meaning. We've avoided the Pandora's box of trying to put a glossary and to define all these terms: What is a vaccine? What is an antigen? What is a combination?

GLODE: We could broaden—I mean, we could deal in the introduction with just the issue that, you know, there are other ways of thinking of combination vaccines like pneumococcus, like OPV that are truly combination vaccines as well.

MODLIN: Jose?

CORDERO: Yeah. I'm okay going one way or the other. I think I just wanted to be sure that when people read this, the definition that they get— especially in the introduction—reflects what it follows in the text. I think that it's really—we just have a discrepancy. Whatever wording we can work out or can be worked out to reflect precisely what's being addressed, I think that that's what we're looking for.

MODLIN: Okay.

WENIGER: To some extent, figure one illustrates the combination vaccines and perhaps helps strengthen the definition. It does include the pneumococcal and meningococcal combination.

CORDERO: I think it needs to be clearly stated in the text.

MODLIN: Okay. Fernando?

GUERRA: I think we have to probably do more than that. I think that it would almost warrant a section in a future MMWR that sort of redefines combinations so that I think the broader audience would pick up on it. I think if we bury it here, I think it will certainly serve the purpose for this

particular statement, but I'm not sure that that will allow us to change the broader thinking that currently exists.

MODLIN: Dave?

FLEMING: I think we may be getting a little bogged down in the semantics here. I view the intent of the statement as really dealing with vaccines where providers have a choice; that is there is a vaccine available with just the antigen that they're concerned about and there's another vaccine available that has that antigen combined with other antigens. In that context, pneumococcal vaccine really doesn't fit. If we expand our definition, I think that the intent of the statement becomes a little bit more cloudy, a little bit more murky. So I would just advocate for whatever the resolution is to be clear about what it is that we're trying to accomplish with this statement.

MODLIN: Yes. Dr. Trump?

TRUMP: Just if you're talking about the pneumococcal as a, you know, single agent vaccine—hepatitis A and some other mentions to varicella—I don't know if those are things you want to remove from the discussion as far as licensed products right now.

MODLIN: I'm sorry. I don't quite follow you.

TRUMP: Well, in the section on interchangeability, you're talking about hepatitis A vaccine, which is not a combination vaccine.

MODLIN: Okay. Good point.

GLODE: Right, and I just want to reiterate what Bruce said is that again, whether or not you think about pneumococcal vaccine as a combination vaccine, we were dealing with it as an example of extra doses of an antigen that may result in increased side effects. So, you know, even if you said, "Well, I don't think of it normally as a combination vaccine," you would think of it as a combination vaccine if it was combined with IPV. All we're trying to do is say to the reader there are some documented circumstances where shortening an interval and giving an extra dose has been reported to result in increased, in this case, local or systemic reaction.

MODLIN: Yeah. Let's come back and focus on the original question here, which was whether or not this extra language is desirable or not. I guess we've heard one or two opinions that it is not. Marie?

GRIFFIN: I guess I don't feel strongly about inclusion or exclusion, but I think if we include it, we should at least delete the last part because I think that

really bogs it down and is a recommendation about—is more detail than we really need.

GLODE: Right. There were really, you know, three options: leave intact, delete completely any reference to it or shorten it by eliminating lines 25 through 31 based on that same rationale, but leave in the reference to it in the boldface and leave in lines 18 through 24.

SCHAFFNER: I think the question is whether or not the addition of one more example helps to make your point any better. I think the key point is the example is given with tetanus. So I'm not, you know—the question you have to ask is does the addition of this paragraph add to the statement in terms of the reader's messages that he or she obtains? I don't think it does. In other words, if you were to read the statement without this example, I don't think that it would be any less strong.

MODLIN: Chuck

HELMS: I'd agree with Georges on that. Unless in this paragraph about pneumococcal polysaccharide there's some sort of disclaimer about "as yet, there is no combination of pneumococcal polysaccharide with another—with antigens of another organism available" because it becomes unclear to me as to why this is being offered as an example. I don't immediately leap to the conclusion that Carolyn has brought out. She's trying to make a, I guess an instructive point, but is this the place to make that point?

MODLIN: I think we all recognize what the dilemma is. Recognizing that, why don't we get a quick—I think probably the best thing to do would be to vote as to whether or not people want to. . .

GLODE: Yeah, and I would say that the choices might be delete all reference to it or the shortened version where the second half of this is deleted.

MODLIN: Okay.

GLODE: Because I haven't heard anybody say to leave it all there.

MODLIN: Those in favor of deleting the entire reference to pneumococcal polysaccharide vaccine? Guerra, DeBuono, Fleming, Helms and Le. Those opposed to deleting the entire reference? It's five. Those abstaining? Okay. Those who—I'm getting a little confused here myself. Okay. Those in favor of retaining a portion of the pneumococcal polysaccharide version? There are three. So it is five to three. We should—we're missing. . .

SNIDER: Mimi Glode.

MODLIN: Mimi?

GLODE: I'd vote to retain it.

MODLIN: I'm sorry. Beg your pardon?

GLODE: I'd vote to retain it in the modified form.

MODLIN: So it is a five to four vote to excluding it completely. Gloria, did you get all that?

KOVACH: Yes sir.

MODLIN: Okay. Sorry for the confusion.

GLODE: Then can we just ask the Committee if we excluded them from—should we also exclude it or just leave it in the boldface, but then not discuss it further? Where we say "extra doses given earlier than the recommended intervals for certain vaccines, however, such as tetanus toxoid and pneumococcal polysaccharide may increase the risk of adverse reaction." Should we delete it or should we leave it in there and then it's not discussed further?

MODLIN: I'm sorry? The consensus is to leave it, I believe. It makes sense; it's educational.

GLODE: Okay. Those were our major questions that we wanted some help from the Committee on. So I appreciate that very much, but now if it's alright, we'd like to open it up to any comments from anyone about the statement. Yes?

MODLIN: Rich?

CLOVER: One minor comment on page 9 on the boldfaced introduction, line 22. You state "An extra dose of most live virus vaccines" and then you specify certain killed antigens. When you read in the detail, you only—on the live vaccines, you specified polio, MMR and varicella. With the potential for approval of other live vaccines, I'm not sure what "most" means any more. I would prefer it to instead of saying "An extra dose of most live virus vaccines," just specify them. Just say "Extra doses of MMR, varicella, OPV, HIV and HepB vaccines have not been found deleterious." It's minor, but it's just—we're going to be approving more live vaccines and the qualifier "most" then becomes an issue.

GLODE: Okay.

MODLIN: Other comments? Tom?

VERNON: I have a question primarily for Bruce. It concerns abbreviations for the vaccines. There are two efforts underway: the one led by Bruce and Jonathan Schwartz here in the U.S. to find standard acronyms to represent the vaccines, and there's also the effort in Europe. I'm wondering if the table here, which lists an entire set of acronyms, is in fact the set that are likely to be adopted by these two efforts—these international efforts—or whether the ACIP is jumping ahead of a process that's underway. Now that the polysaccharide acronym is no longer in the text, it could be dropped from the table and doesn't challenge whatever these subsequent efforts might adopt. I do wonder about whether the ACIP is ready to jump onto PNPS, for example, as the standard acronym for pneumococcal polysaccharide vaccine.

WENIGER: The answer to the question is that we do not have any final set of abbreviations to propose under that initiative. We got in touch with the Europeans when we learned recently that they also had an initiative to create abbreviations which were somewhat different than the ones we had been drafting and beginning to circulate. The short answer is no, these are not any kind of a final form of proposal. The principal reason for having this table here is simply to save a lot of space in the document itself. When you first mention a vaccine and start immediately with an abbreviation, I think clearly any vaccine that's no longer mentioned in the document can be left out; however, I think currently we're going to change to the PN—the pneumococcal abbreviation to PNUCON or PNUPS, but these do occur in the figure. So having them in the figure sort of justifies leaving them in this table. This is not proposed to be any kind of a formal recommendation that these are official abbreviations.

MODLIN: Are there additional comments, questions? Rick?

ZIMMERMAN: I think one of the main questions is process. Where are we going to go from here? At what point are we going to ask the editors from the three different journals to look at it? At what point are we going to ask the boards to look at because obviously, the boards don't want to look at it twice. They want to do it once once we've got things. So I guess discussion of when we're going to do the process stuff would be helpful.

HALSEY: Mimi, can I propose. . .

GLODE: Yeah.

HALSEY: I think we can probably work that out in a smaller group of the three different things, rather than the entire Committee spending time on that.

I think because that's a process issue; it's not a substance or policy issue.

MODLIN: I was going to make exactly the same point. I think this Committee needs to be focusing on the specific policy here—what's in bold. I think that we can manage that today hopefully.

GLODE: Right.

MODLIN: As with rotavirus, with the recognition that there will continue to be changes in the editing and the word smithing of the document. I don't think that that bothers anybody. Again, other issues, any issues regarding the combination vaccine statement at all?

GUERRA: John, I'm not sure how to state it, but I want to be sure that as we work through the statement, that we don't end up imposing so much of a burden on the individual health care providers in terms of the inventory that they may be expected to maintain with so many different products. I think that on page 8 in the vaccine supply, I think that probably is okay, but I just am trying to make sure that when this gets out to the much broader community, that physicians— especially the smaller practices—know that it's okay to maybe have one or another product and not have to worry about a lot of the others. In the instance where, I think, that we have given some license to be able to—if one has to interchange products, that maybe we could again make reference to that in the supply. It may not be a concern other than I think that. . .

MODLIN: But I hear that you're quite comfortable with—you feel that the current language for the most part achieves that objective?

GUERRA: I just want to be sure. Maybe we can accomplish that in another section; maybe in part of the introductory comments. I think that, you know, it's incumbent on us to be sure that we don't add to the tremendous layer of cost that physicians, or practitioners or health care providers are having to bear these days because of all of the changes that are taking place.

MODLIN: In other words, can this language be supported in other portions of the statement? I'm not exactly sure where those portions would be, but you know it better than I do.

GUERRA: Yeah.

GLODE: Yeah. I mean, right; I mean this particular three sentences I guess, you know, the Committee spent a lot of time trying to achieve the right balance in this statement.

GUERRA: And it may be there, you know. I just—I guess one needs to see how it plays out.

MODLIN: Okay. Other comments? Peter?

PARADISO: Yeah. I would just like to make a general comment. I talked to Mimi about this before. I know that this statement has, you know, been through thirteen versions. I read the last version. My concern reading through it is I come away with a sense of trying to make generic comments about what's going to end up being applied to specific products. It seems to me that you run into some trouble doing that and you may create confusion doing that, you know. I specifically would refer to the fact that it's okay to interchange, but then, you know, there are equal numbers of vaccines where you're comfortable doing it and an equal number that you're not. It's okay to give extra doses, but in fact, there are an equal number that you can give extra and you can't give extra.

In fact in the example, all DTP combinations seem to be under the category that you can and, you know, that's sort of a mainstay of what we're doing. I'm not sure that sometimes we can reconcile what's in here with what's out there and what's in your other recommendations. I think you have the potential for causing some confusion here when you try to relate back to those individual products, you know. The last—I guess the last comment would be related to something that I guess was discussed yesterday morning before I got here; was that, you know, if you over-emphasize combinations at any cost, then you have the potential of encouraging the use of combinations that are not combinations and people putting together things like DTaP and Hib that were not licensed to put together for the purpose of using combinations. I just, you know—it's just a reaction I have when I read the statement and I just wanted to express it here.

MODLIN: John?

LIVENGOOD: Well, I think one thing in particular I've gotten out of this morning's discussion is that we have to be prepared to, at least to the states' issue, a question and answer set about what some of these things mean. Because we've negotiated so carefully where to insert which word and which clause out of some of these recommendations, that I think we're going to have to follow-up with some instructions that are a little clearer with some of these other examples and some of those concerns because actually, I agree with that; that we've tried to write it. We've gotten so carefully generic and everything, that I think at least some readers are going to get lost at certain points about "what are you actually trying to do with this statement" and some of these questions. I know at times I've expressed those things too. So I think that probably

we ought to, in collaboration with the other people issuing this statement, come up with some questions and answers set that we can send out to states with some specific examples. "Well, here's what we mean about some of these things" in a little more detail where we can be a little more specific about what combinations or what individual types of vaccines we're talking about. Rather than putting it out as an ACIP statement, treat it as programmatic guidance where we can send to a program manager and say, you know, "You don't have to call us and ask this question. Here's what we think the answer is."

MODLIN: The particular advantage of that approach, of course, would be that you can change those questions and answers readily without coming back to the Committee and changing the statement, which makes a lot of sense.

GLODE: That was the other point Peter mentioned to me yesterday; was that, you know, you're trying to write a statement without exactly knowing the future. So you're trying to make these generic statements about come combinations that don't—are not licensed and in use yet. Yet you're hoping it will apply to it. We did—I just want to, we are concerned about people doing their own combinations. We did deal with that specifically in the document at the bottom of page 4 under a section stated ***Combining Separate Vaccines When Not FDA-Approved***, and tried to at least put that caution in there pretty directly.

MODLIN: Fernando?

GUERRA: One other is just an observation that we have made in the immediate short-term of the availability of the Comvax, which is the combination of Hib and HepB; and that that has sort of gone counter to the efforts that have been at least initiated in some local health departments to try to promote and increase the uptake of the prenatal hepatitis A in a population of newborns. As that has gained perhaps, at least more in the private sector network, some increase in uptake for the combination by pediatricians that perhaps don't see so many of the Medicaid managed care patients, we have noted a decline in the number of doses that are given in newborn nurseries because they just postpone it and give it at the time of the office visit. So whether or not that's going to have any long-term consequences, I'm not sure yet, but that is something that we've observed.

MODLIN: Thanks. Okay. Hearing no other comment, I think it is time to entertain a motion that the ACIP vote to accept this version of the combination vaccine statement. It's been moved by Dr. Fleming, seconded by Dr. Helms. Okay. The motion is on the floor. Dr. Clover?

CLOVER: Are there any conflicts of interest that need to be addressed?

MODLIN: People are—we're either all conflicted or none of us are conflicted the best I can tell. I think the practical. . .

SNIDER: Unless I'm told that I don't have discretion, you all can vote.

MODLIN: I think the practical matter is is that everyone is eligible. Okay. Those in favor of the motion? Those opposed? All voting members present voted for the motion and the motion carries.

GLODE: Thank you very much.

MODLIN: Bruce, thank you very much and thank you to the working group for a job extraordinarily well done. We've gained a little time. We may need it; we almost certainly will need it for the Lyme disease vaccine. The suggestion here would be to take a break. Let's start back at ten minutes until, at 9:50. Let's begin the Lyme vaccine session at that time.

Can I ask everyone to be seated please? Just a couple of quick announcements before we get started. Dr. Guerra has just asked me to announce that there will be a working lunch for the influenza working group, which will be located in one of the. . .

GUERRA: Room 1111A of the new building.

MODLIN: Thank you.

SNIDER: Very close to the cafeteria, very close to the elevators.

MODLIN: Secondly, we are in the initial phases of forming a working group on adult immunization that Rich Clover has graciously agreed to take on as chair of the working group. We have a couple of members who have volunteered, including Dr. Schaffner and Dr. Gardner. There will be others added to the working group. If there are individuals who are interested in joining the working group, please let me know. We want to make it representative, but still small enough to be workable. So if you'd let either myself or Dr. Clover know, we will complete that. Rick Zimmerman, Dr. Guerra, Dr. Helms—and terrific; that's a good start, and Dr. Gall, I'm sure.

SNIDER: What about HepA?

MODLIN: HepA we still need to talk about. I guess that's it. Let's move on and begin the session on Lyme. This will be the first session on Lyme vaccine which has included any real discussion by the Committee. We have had presentations, at least on one occasion—I believe on more

than one occasion—from both SmithKline and Pasteur-Merieux Connaught on updates on the progress of Lyme vaccine development. A working group was formed at the conclusion of the February meeting that has been headed by David Fleming. They are going to— they've been extraordinarily active and they're going to be leading us through the discussion this morning. I think Dave will make this point, but I will as well that in these initial stages, that we want to be focusing as much on the process by which we're developing the Lyme statement as the details of the statement itself. Dave?

FLEMING: Well, good morning. I don't see the lavaliere here, so I'll just use this microphone. Oh, here it is. I just wanted to give a few introductory comments. The good news is that I promise that they'll be brief and they'll almost certainly be the low point of the next two hours because I think we're in for a really exciting session regarding thinking about how we're going to be proceeding with recommendations for Lyme disease. The goal of the next hour and a half to two hours is not to provide you with a lot of generic information about Lyme disease. We've done that already, as John mentioned, in a couple of previous sessions. The Committee members have received extensive background information on the vaccine issues around Lyme disease.

Instead what we really want to do in this session is to get some fairly focused input from you regarding your sense for the directions we should be taking with the Lyme disease recommendations. Specifically, we'd like to concentrate, for lack of a more artful term, on the guts of the recommendation today. By that, I mean the critical constructs regarding what we're going to be saying about this vaccine and how it should be used. If we have time—and I think we will— after we've had that discussion, we are going to be moving on to a more explicit discussion of two issues: one, recommendations regarding use in children and second, timing of doses. Again, the critical issue initially is to get some general input on the direction.

This is always a challenge. There we go. At the outset, I just did want to acknowledge the fact that we have had a very expert working group. It's big as you can tell by the fact that I can't get all of the people on it to show at the same time, but include members not only of the Committee and liaisons, but experts from state health departments, from the manufacturers and from the clinicians seeing patients with Lyme disease. I'd like to especially acknowledge the work of Dave Dennis and Ned Hayes in coordinating us. Well, I think the main issue that we wanted to talk about was that as we've seen at least partially with rotavirus, a randomized trial showing safety and efficacy of a vaccine is not all of the information that we need to consider in developing recommendations regarding vaccine use. I think that's particularly the case for Lyme disease vaccine. I think it's the sense of the working

group that we need to pay great attention to other potential determinants of vaccine use: to use expert opinion and to use potentially some of our collective sense of common values in developing ultimately our recommendations for this vaccine.

What we'd like to do first is have about a 45-minute presentation of information about the vaccine and then discussion. Just a few minutes to orient everybody at a time, place and person about the vaccine; so about three minutes update on the vaccine itself. Then we're going to have about fifteen minutes discussion from the FDA on safety and efficacy issues as were discussed at the last FDA Advisory Committee. We're then going to move on to our presentation about risk of Lyme disease in this country—not only geographic, but occupational and recreational, and other issues that might influence how we recommend this vaccine to use, and finally finish with some information about cost effectiveness of vaccine use. I'm going to give away the ending on this and hopefully, everybody has this on the Committee and the liaisons.

What we really would like to do is have you be listening to these presentations in the context of this straw-person proposal for directions that we need to be moving with Lyme disease. At the end of that 45 minutes, we're going to be explicitly asking you to comment on the nature of the recommendations as described here. The first is we want your input on our sense that in essence, Lyme disease is probably not a vaccine for which universal use is appropriate. It's also probably a vaccine that at least some people should be getting. So in that context, it's our sense that really a person's risk of the disease is the primary determinant of whether or not they should be getting this vaccine. So what we're looking at here is a risk-based recommendation for persons aged fifteen to seventy. Assuming that that's the direction that we all agree we should go, the next question is, "Well, how many levels of risk should there be?" We want a recommendation that is both accurate, but sufficiently simple that clinicians and others will be able to follow it.

One proposal would be to divide risk into three levels and that's what's shown here. Alternatives would be two or four or some other number, but basically, something to react to would be to have three levels of risk: a risk that's high, medium and very low to zero. A critical issue that we want you to think about is when you're thinking about the number of levels of risk that should be in this statement, we want there to be a one-to-one match with the strength of the recommendation. We don't want to define more levels of risk than we're prepared to say how the vaccine should be used differently given those different levels. So whatever number we come up with needs to be matched to what we're going to be saying about vaccine use for that level of risk.

Again, just as a straw-person proposal, for the highest level of risk, one idea would be to have language sort of a "should be considered" or "is appropriate" kind of language for that level of risk. For the medium level of risk, sort of a much more permissive, "if you want to give it, it's okay; may be considered" kind of language. Then for the very low or zero risk, a "not indicated." Again, these are just proposals, but I wanted to give you some context for reacting. Assuming that we do go with the level of risk in different levels, the third issue to consider is what are the determinants for what the cut-off should be for those different levels of risk. This is a very difficult issue.

We want you to consider the extent to which those risk cut-offs should be based loosely on cost effectiveness as a potential difference between highest and medium—sort of a reasonable cost effectiveness being the determinant there—and from the medium to very low, an upper margin of what we're willing to consider as the amount we're willing to spend per case prevented. Then finally for the rest of the statement, there are going to be a number of issues that we will be coming back to at the next meeting. I think the working group's general inclination is not to diverge substantially from the FDA language and the package insert on most of these other issues. So having said that, I'd like to invite Dave Dennis up to give you the brief initial introduction about the vaccine. Dave?

DENNIS: Good morning. David had asked me to just very briefly review the safety and efficacy of the vaccine that has been now tried at a large scale field level. I will give just a few introductory comments to that. The process of developing a vaccine for humans against Lyme disease has been going on now for about ten years. Fairly early on, the researchers and manufacturers settled upon recombinant protein for use in vaccine that was specific to an outer surface protein of the organism *Borrelia burgdorferi*. The outer surface protein A has been the protein that the vaccine has centered around. So I think it's important to understand that this vaccine is effective against organisms that are expressing this outer surface protein A and they don't do that throughout their life cycle.

The other thing is that it's important to understand the epidemiology of Lyme disease in that it is a tick-borne zoonotic disease. Humans are only dead-end hosts who become infected when they accidentally intrude into the natural enzootic cycle. They neither serve as a reservoir of infection for maintenance of the cycle of the organism in nature, nor do they transmit the organism from person-to-person. So it's a non-contagious disease and it's a disease for which a vaccine wouldn't be expected to reduce the reservoir of infection in a community. There have been a number of studies of the recombinant outer surface protein A vaccines in humans, and of course, many

studies in animals. The studies in humans have looked at, of course, the basic safety and immunogenicity, looking at the cause of immunogenecity and protection, looking at dose ranging, looking at the value or not of adjuvants.

As it turns out, there are two vaccines that have gone the whole process from Phase I, Phase II and through Phase III trials: one by SmithKline Beecham, the other by Pasteur Biomerieux. They're both recombinant outer surface protein A vaccines as I said. They're both lipodated: the SmithKline Beecham vaccine used as an alum adjuvant and the Connaught does not. SmithKline Beecham presented their Phase III data to the FDA. The FDA Advisory Panel has met to consider their safety and efficacy at a meeting on May 26th. Karen Elkins will be able to describe for you the details of the presentation, as well as the important aspects of the discussion of that meeting. Connaught as well has submitted their data to FDA and are awaiting the opportunity to present that to the FDA Advisory Committee.
I'll just give a brief breakdown of the efficacy first. The SmithKline Beecham product, LYMErix, underwent the pivotal Phase III trials over a period of twenty months of observation, enrolling almost 11,000 subjects, aged fifteen to seventy years, recruited at 31 sites in New England, mid-Atlantic and upper north central regions. The vaccine was given in three doses at a schedule of 0, 1 and 12 months. The 0 and 1 was given to be able to provide the greatest immunogenecity or protection in advance of the first year transmission season that, in Lyme disease highly endemic areas, is mostly from May through July and through early as August. That's the peak transmission season. The month twelve or so-called booster dose was given shortly before the onset of the transmission season in the second year.

So if we look here at the vaccine efficacy in preventing definite Lyme disease in all age groups—fifteen through seventy—after two doses, you can see that it was only 50 percent efficacious in that first year. In preventing asymptomatic infection as determined by sera bleeds, and looking for seroconversion in persons who did not report or did not have detected any illness that was thought to be Lyme disease, it was 83 percent protection in that first year. After the third or booster dose—and it had been shown there was a big jump in immunogenecity after that booster dose—the protection against definite Lyme disease was almost 80 percent in that second year and against asymptomatic seroconversion was 100 percent. For both protecting against definite and asymptomatic Lyme disease in persons aged fifteen through 65—and a cut-off was made in this analysis because persons older than 65 seemed to have a lessened protection, particularly in the first year, and the data were not robust enough to really fully understand that—if we look at the fifteen through 65, then there was 60 percent protection after

two doses or year one, and 90 percent protection after three doses or year two.

The Connaught product—a very similar product as I say except that it did not have an alum adjuvant—they as well, their pivotal trial was a randomized clinical trial obviously in over 10,000 subjects aged— equal to or greater than eighteen years. They did not go down to fifteen years as the SmithKline Beecham. They recruited fourteen sites in New England, mid-Atlantic and north central regions as did the other manufacturer. The vaccine was given in the same dosage as scheduled. Their vaccine efficacy after two doses in year one was about 66 percent. After three doses, it was a little over 90 percent for protection against definite Lyme disease. I haven't seen the data yet for protection against asymptomatic seroconverters for that trial. I will say that we are at some disadvantage today because we're a little bit preliminary in that the results of neither of these trials have been yet published. Both have been submitted; I understand both have been accepted to publication and we hope that the published data will be available shortly.

I'm going to just briefly summarize the safety data as determined by the pivotal Phase III trials. Obviously, there was increased incidence of adverse effects in the vaccine recipients compared to placebo only in the first week or so after administration of the dose. These adverse effects were most frequently reported: pain in the injection site, and tenderness, myalgia and arthralgia. These were mild and self-limiting. There were no serious adverse effects identified that were associated with vaccine administration. There were no deaths attributable vaccine; there was no serious hypersensitivity reaction to the administration of the vaccine. There are other issues related to vaccine safety over the long-term that have to do with some theoretical considerations that were discussed in some depth at the FDA Advisory Committee meeting. Karen Elkins will be providing us with information on that. Thank you.

MODLIN: Dr. Elkins?

ELKINS: If someone could put on the slides back there. I have to apologize. I had a small summer cold that left and took most of my voice with it. So if you could bear with me, I'd appreciate it. I would like to try and summarize the discussions by the Vaccines and Related Biological Products Advisory Committee which took place on May 26th. This is one of CBER-FDA's several advisory committees that provide input, obviously, on vaccine-related issues. On May 26th, we specifically asked them to consider the safety, efficacy and seasonal use of Lyme disease vaccine from SmithKline Beecham. This was the only data discussed at this particular presentation. We also asked the committee

to provide advice in the use of the vaccine in persons over seventy and on any additional studies which should be considered later.

To reiterate, this is a recombinant protein, specifically outer surface protein A which is lipodated. The particular formulation under consideration was 30 micrograms and a half a milliliter of a PBS buffer absorbed to aluminum hydroxide and containing 2-phenoxyethanol as a bacteriostatic agent. It has been of interest, as Dr. Dennis mentioned, for some time because it has been shown to be protective in various animal models. In addition, monoclonal antibodies, as well as human sera containing anti-OspA antibodies, are able to transfer protection to mice that are subsequently challenged with virion *Borrelia*. Well, that's on the plus side of OspA. On the minus side of OspA has been this association of anti-OspA immune responses in treatment-resistant chronic Lyme arthritis, which is a relatively rare complication of late Lyme disease in which arthritis persists despite apparently appropriate antibiotic treatment and elimination of bacteria. This has led to the suggestion that the anti-OspA immune response may in fact be an anti-cell for autoimmune response.

Specifically, treatment-resistant chronic Lyme arthritis has been associated with the development of anti-OspA antibodies, which generally appear late in disease. In further treatment-resistant Lyme arthritis has been associated for certain Class II major histocompatibility genes, notably particularly DR4 and DR2 alleles. This might lend itself to a cell-mediated pathogenesis. There has been some very recent data that's about to be published that lends further support to the latter possibility; that is that a cell-mediated immune response that is autoimmune in nature may be involved in the pathogenesis of treatment-resistant Lyme arthritis. One group has identified an epitope in OspA that shares homology with an epitope in human leukocyte function-associated antigen 1, or LFA1, which is present on all human lymphocytes and particularly on activated T cells that might be present in the inflamed joint.

However, it's not clear what the relevance of these observations are for vaccination with OspA. In the clinical trial, there was no observed increased in incidence in arthritis in vacinees as compared to placebo recipients. So based on the plus side of OspA, and with hopes for the best on the con side of OspA, SmithKline selected this particular formulation based on initial European studies. The USIND was initiated for Phase II trials in 1994. The pivotal Phase III trial was conducted over 1995 and 1996. The license applications for this product were submitted in 1997. Bridging studies for final manufacturing scale-up were initiated in 1997 and completed in 1998. So the questions that were put to the Advisory Committee were as follows. First, "Are the

data sufficient to support the conclusion that the vaccine is safe for immunization of individuals fifteen to seventy years of age?"

I couldn't begin to do justice to summarizing the safety data. Dr. Dennis has given you a fast taste of it, which I would reiterate here the vaccine was evaluated in the pivotal efficacy trial of over 5,400 people over twenty months of blinded following another four months unblinded. The A's indeed were mostly injection site related or when systemic, were short-term and self-limited. One area worth mentioning is that there was a higher incidence of musculoskeletal events in vaccinees as compared to placebos when either of those groups self-reported a previous history of Lyme disease. That was within thirty days after vaccination. However, that difference did not persist at greater than thirty days post-vaccination. There was no such difference between vaccinees and placebos who were seropositive at baseline by western blot for a previous history of Lyme disease, which is a somewhat different group.

So based on the data presented, the VRBPAC vote was "yes, but" with the now famous stack of provisos phrase thrown in. The provisos first of all assumed that the vaccination schedule would be 0, 1, 12 months and without further booster doses until further data become available. There was a great interest in large-scale intense long-term follow-up of vaccinees with the thought that 20 to 24 months may or may not have been sufficient to reveal any late serious AEs and/or that the group size may not have been large enough to protect rare AEs. There were a number of cautions for those that excluded from the pivotal trial Those excluded included people with active or recent Lyme disease, people with chronic joint problems, people with a high degree of AV heart block or pacemakers, as well as pregnant women. Since there are no data available, particularly ones related in joint disease, there is a great interest in caution for those kinds of groups. There was a great deal of interest as a corollary and more study in those with a Lyme disease history or recent active infection.

The second question concerned efficacy and was stated as "Are the data sufficient to support the conclusion that the vaccine is effective against definite Lyme disease in individuals fifteen to seventy years of age when given on a 0, 1, 12 month schedule?" Dr. Dennis has already shown some of this data, but there's one category that's mentioning as well. Definite Lyme disease, or category 1, was defined as an appropriate clinical picture, principally erythema migrans with laboratory confirmation of infection. The protection in the first year, as Dr. Dennis noticed, was 50 percent, but the lower confidence bound was 14 percent—rather low. A second category or probable Lyme disease was subdivided into two subsections. Category 2.1 was erythema migrans greater than five centimeters but without laboratory evidence of

infection. Category 2.2 were those that had a non-specific clinical picture—clinical symptomology—such as flu-like symptoms, but which converted by western blot. As you can see from the case numbers here, they're fairly small, but there really was no compelling evidence of protection in either of these two categories. The actual calculation was not statistically significant.

The final category, 3, was asymptomatic seroconversion. Here, the vaccine efficacy in year 1 was 83 percent with a lower confidence bound of 25 percent. In year 2, particularly in definite Lyme disease, the numbers were more compelling. Where the category 1 protection was 79 percent with a lower confidence interval of 61 percent, but again in the probable Lyme disease, there was really not a very compelling trend, particularly in category 2.1 with erythema migrans only a little more of a trend out of eighteen cases for the western blot seroconversion cases. However, this also did not achieve statistical significance. In category 3, there was 100 percent protection with a lower confidence interval of 30 percent. So in answer to the efficacy question, the VRBPAC also came to the "yes, but" conclusion. The first "but" concerned interest in the same limitations as in the safety questions; that is that the schedule be considered 0, 1, 12 months and that the efficacy be described as those only that were included in the trial, not those that were excluded.

I think the Advisory Committee was satisfied that protection against category 1 disease was not demonstrated; however—it was demonstrated; I'm sorry—but that there was no protection against probable disease. There was a feeling that at least a number of the cases in that probable disease category were indeed Lyme disease. The erythema migrans in category 2.1 could of course be a confused rash, but a number of them probably were legitimate erythema migrans. In the category 2.2s, there were probably some seroconversions due to infection with Ehrlichiosis, but again, there were probably a number that were real disease in there. So the evidence here is confusing. The Advisory Committee was uncertain about the clinical significance of protection against the asymptomatic infection, although the numbers were indeed compelling. The third question asked not for a vote, but for advice and was phrased as "Please comment on the use of Lyme disease vaccine in persons over seventy years of age."

There was a great reluctance to include persons over seventy in the labeling and expressed interest, great interest, in bridging studies to this population. There is a significant amount of disease, particularly in the active seventy- to eighty-year old populations, but there is some trend toward lower antibody responses at least in this population. So thus, there was an interest in bridging studies before extending the use of vaccine to persons over seventy. Similarly, there was very strong

comment on the use of vaccine in children under fifteen and that is that they should definitely not be included in labeling until safety data become available. Previous Advisory Committee deliberations have been quite specific on the point of using this vaccine in children in that safety and efficacy should be demonstrated in adult populations and an acceptable risk benefit relationship defined before trials were initiated in children unless those are only recently underway.

Question 4 concerned the seasonality of infection in as follows: "In the efficacy trial, vaccinations were given just before the *Borrelia burgdorferi* transmission seasons at 0 and 1 month between January 15th and April 15th, and then twelve months later between approximately February 15th and April 30th. Should a similar seasonal vaccination schedule be recommended in the package insert?" The answer here was a strong yes. This schedule was probably originally assigned to maximize efficacy such that immune responses might be highest as persons entered the tick transmission season. The Advisory Committee also reiterated that the schedule was of interest for safety reasons as well; that is vaccination in the late winter and early spring months would be most likely to avoid vaccinating somebody who had as yet undiagnosed Lyme disease, which could be a safety issue.

Number 5, "Are there any additional studies that should be performed by the sponsor?" As you might infer from the previous deliberations and all those stack of provisos, these all came up again in this question with a laundry list of studies that were of interest. Many of these hinged on the definition of a serological correlate of protection. Those data are still under discussion and review and will be forthcoming at a later time. As already mentioned, there was, again, great interest in large-scale longer-term follow-up for safety. There's an interest in specific studies designed in older and younger age groups. There's an interest in the duration of protection with the schedule, which after the second Lyme disease transmission season is unknown; an interest obviously in the need or use of booster doses after the 0, 1, 12 month schedule or in alternate schedules altogether. There's an interest in studies in the groups that were excluded the first time around, particularly those with chronic disease.

DENNIS: Does anybody have any questions?

MODLIN: I mean, are you pretty much finished? Dr. Dennis, are you pretty much finished this portion of the presentation?

FLEMING: John?

MODLIN: Yes.

FLEMING: I think our intent here. . .

MODLIN: I'm sorry.

FLEMING: I think our intent here was to allow questions on specific issues, but not to try to get into the more general question of what the recommendation should be until the end of all of the presentations.

MODLIN: Terrific. So let's do entertain questions. If we could have the lights, please, and we can begin entertaining questions specifically on these presentations. Is there a question about process, Stan?

GALL: No, not about process. What do you do about pregnant women that live in the upper midwest and the northeast?

MODLIN: Okay.

GALL: Do they ship them all out of there during the summer?

ELKINS: Well, the best I can say is that there's no data available. Pregnant women or women who are intending to become pregnant were excluded from the pivotal trials. There are reproductive animal studies being contemplated at this time, but there is no data available yet.

MODLIN: I think those of us who are advocates for pregnant women. . .

GALL: So you want them to all have Lyme disease?

MODLIN: Those of us who are advocates. . .

ELKINS: I wouldn't infer that, no.

MODLIN: Those of us who are advocates for pregnant women and for children, I think, would have some concerns about the sequence and the conduct of these trials. Let's focus if we could. . .

ELKINS: One of the—if I could make one comment, there was one point that was well taken at the Advisory Committee meeting, which was that this is a molecule that carries its own adjuvant. It's lipodated and it has been shown to be proliferative for human B cells and to induce cytokine secretion endothelial cells. So the impact of that on a developing fetus is of concern.

MODLIN: Okay. Pierce?

GARDNER: I just have a request of the wonderful presentations. I'm wondering if we could get copies of the slides as we got for the hepatitis presentations yesterday. That would be useful. I think the process as

outlined by David Fleming was terrific and I appreciate this wonderful presentation.

MODLIN: Okay. We'll begin with the inner table at the moment and go around. Chinh?

LE: The studies were done in 1994 through 1995.

ELKINS: This particular one was 1995 to 1996.

LE: Yes, 1996. Two years later, I'm still surprised you don't have serological correlates of disease protection actually measuring anti-OspA antibodies. I think it should be available to us by now.

ELKINS: It's not. The data is still under review and has not been—certainly, we have not come to consensus on that.

MODLIN: Georges?

PETER: Well, the first question is related to the serology, which of course, when you're involved in caring for patients in an endemic area, it's a major, major problem. I am concerned about the problem of differentiating between infection and the serological response to the vaccine. I realize that's an issue. I wondered how far along are we in terms of coming up with better tests? Because I think this is going to be a true problem in implementation and use because one of the major problems clinically is over-use of antibiotics over ordering of tests when you live in an endemic area. The second point is really one, again, along the lines of what John Modlin said. As advocates for children, how far along are the studies in children? It's going to be very difficult with respect to if the vaccine is licensed for young adults and then they want to know why their eight-year old who's in the highest risk group cannot receive the vaccine. I realize that you don't want to approve the vaccine until you have studies, so my question really is what's the status? When can we expect results in children?

ELKINS: Well, the pediatric trials are just this month underway. Obviously, it'll take some time to accumulate data and to review it. We are, as you are, quite concerned about potential off-label use in pediatric population. Again, this is a lipodated molecule of unknown safety implications for smaller, younger people. Clinicians would need to bear that in mind in making any such decisions I would say. With regard to the diagnosis, there has been data—the manufacturer may wish to speak to this—that shows the expected; that is that persons vaccinated with OspA have sera that test positive in several of the commercial ELISA kits. Most of those kits use cold *Borrelia burgdorferi* grown *in vitro* that does indeed express OspA on its cell surface. So as

expected, they become false positives in the commercial kits. However, the OspA band is not part of the standard criteria for interpretation for western blots. So vaccination does not confound western blot interpretation. Of course, that is a more expensive possibility. It's my understanding that there are kits under development that use OspA-negative, OspB-negative *Borrelia*, but I don't think those are very far down the pipeline.

MODLIN: Dave?

FLEMING: I just wanted to comment that a focus of the first part of these presentations is for use in fifteen to seventy. After we finish with that discussion, and hopefully we will have time, we will have a brief discussion on use in children. So we can defer that discussion until then.

MODLIN: Terrific. Paul?

GLEZEN: I had a question in relation to safety of the vaccine and chronic arthritis. I couldn't find it in a quick perusal of the information. Is the disease—does it have selection variables related to gender or age? I'm talking about chronic arthritis.

ELKINS: Treatment-resistant chronic Lyme arthritis?

GLEZEN: Yeah.

ELKINS: Age and gender, I don't believe so, although somebody else may know that data better than I do. The biggest identified risk factor is containing certain DR4 and DR2 alleles. Those are actually the ones that are usually associated with rheumatoid arthritis. If you're familiar with that series, that seems to be a large predictor for risk factor. Certainly not all people who have DR4, which is the major allele implicated, will develop treatment-resistant chronic Lyme arthritis.

GLEZEN: Yeah. Well, my question would be did enough people with those characteristics receive the vaccine so that you can. . .

ELKINS: Well, a large percentage of the population that received the vaccine would indeed have been DR4 or DR2-positive. However, in disease itself, it's not likely that a large percentage of people that are DR4 or DR2-positive develop treatment-resistant chronic Lyme arthritis. The other factors that may lead to that unfortunate outcome are unidentified. The issue, I think, is whether or not vaccination with a recombinant single protein might in some way mimic the entire series of unhappy events that culminate in treatment-resistant Lyme arthritis and that's unknown.

MODLIN: Chinh?

LE: The efficacy result during the first year, after the first two doses were only about 60 percent or so, right?

ELKINS: Fifty percent with a lower confidence interval of 14 percent.

LE: My question is are those cases of failure, vaccine failure, break-through early disease, which is incubating at a time of the vaccination, or whether this happened way in the back?

ELKINS: No. Actually, the efficacy period was defined as one month after the second vaccination. In other words, the window for definite cases had to be three days afterwards. There were a couple of cases that developed in the first thirty days that were probably incubating at the time of vaccination, but those were not included in the efficacy analysis. Quite a number of the ones that developed in category 1 over that first year were in June and July with the same sort of seasonal pattern as non-vaccinee cases. So there was no shift in the timing of detection of cases detectable.

MODLIN: Questions? Fernando.

GUERRA: Yesterday, some reference was made to this being a “yuppie” vaccine. Did the study population include a more diverse group of individuals, recognizing that there are a number of seasonal and migrant workers that move up to the northeast during parts of the year? Were any included or others that have settled out?

ELKINS: Well, the manufacturer may be in a better position to answer that than I am, but the study centers were in the northeast and one in the upper midwest. So I would suspect that not too many of that category would have been included. They also had to be resident over the course of thirteen months of course.

MODLIN: Let Dr. Parenti speak.

PARENTI: They didn’t have to be residents over the thirteen months. They did have to be in an endemic area for the tick season. So theoretically, we could’ve had some snowbirds, for example, but basically these were residents in endemic areas and represented the typical population in that area, which turns out to be approximately 98 percent Caucasian.

MODLIN: Thank you. Any questions? Georges?

PETER: I think if I understood correctly, you mentioned that some persons who had had past Lyme arthritis indeed had a higher incidence of musculoskeletal complaints, but it was self-limited.

ELKINS: Not exactly. The higher incidence of musculoskeletal events was in people who self-reported a past history of Lyme disease. That could be any sort of disease, Erythema migrans, that was treated and eradicated on the spot.

PETER: Okay.

ELKINS: Right, and you know, the self-reporting nature of that leaves it uncertain as exactly what that group compromises.

PETER: Well, my question was did those individuals have a different antibody response in terms of quantity of antibody to the vaccine than those who did not have that history?

ELKINS: Not detectably, although those with the data would be better prepared to give specifics.

PARENTI: We looked in both safety and immunogenicity by two criteria: whether people have a self-reported history of Lyme disease or whether they were positive at baseline by western blot. As far as immunogenicity is concerned, if you look at those two populations, there's no difference in their immunogenicity. With regard to their safety, it's a little bit more complicated. If you look at the people who have a positive western blot at baseline and look at the vaccinees compared to those who don't have a positive history—a positive western blot at baseline—we found no statistical difference between those two groups. Now for the groups that had a self-reported history of Lyme disease and compared the vaccinees to those who didn't have a self-reported history, yes, there was a higher incidence of not only musculoskeletal complaints, but other body systems as well, including psychiatric and GI complaints.

If you look at the people who were placebo recipients and those who had a self-reported history of Lyme disease versus those who didn't have a self-reported history of Lyme disease, you found the same pattern. The people who had a previous history of Lyme disease had a higher incidence of musculoskeletal complaints, psychiatric complaints and GI complaints. I don't know how to interpret that. People who had a previous history of Lyme disease had more complaints, I think summarizes it.

ELKINS: That difference, such as it was, was at less than thirty days. It did not continue to greater thirty days observation. People who had any Lyme-

related arthritis were excluded from the trial. So there would not be data to that effect.

MODLIN: Chinh?

LE: I guess along that same population of people who had Lyme disease before, is your study large enough in number to know whether the people who had Lyme disease before were protected by this vaccine from subsequent disease in the future?

ELKINS: I'll say the power there is a little shaky.

MODLIN: One of these trials was. . .

ELKINS: Do you want to comment, Dennis?

PARENTI: Just to say that if we looked at either people who had self-reported history of Lyme disease or people who had a previous western blot, we have definite cases of Lyme disease in those groups. We have cases of people who got Lyme disease in both years for example. We have cases of an individual who was infected twice during the same year.

LE: But was this vaccine protective in those people?

PARENTI: Well, again, as Karen mentioned, it's a small population.

ELKINS: There were about 125 vaccinees and placebos in the western blot-positive and about 600 and 600, I think, in the self-reported history.

MODLIN: Might I ask if one of these trials were conducted so that we've had three years since then, do we have any information on follow-up beyond the second year of the trial that you can share with us in term of efficacy?

ELKINS: Well, the SmithKline trial did have a design for follow-up into this season and those data are just becoming available. Do you want to comment on it?

PARENTI: We did follow a very small cohort of people into the third year without giving them any additional booster doses. Unfortunately, that turned out to be 1997, which was not a terribly busy tick season. So we actually had very, very few cases. The numbers were very, very small to begin with, so we really essentially do not have data for. . .

MODLIN: Beyond the second year?

PARENTI: Yes, as far as efficacy is concerned. We continue to follow those subjects for safety.

ELKINS: I know that follow-up is always difficult.

MODLIN: I understand. Chinh?

LE: Yes. Two quick questions. Do we have anybody from Connaught Vaccine here just because their study is just as big and whether they can add something to the questions and answers? Secondly, is this vaccine expected to be protective in other parts of the world, Europe, where the type of Lyme disease is a little bit different?

ELKINS: No. The OspA protein was from actually a German strain, but a *Borrelia burgdorferi* sensu stricto isolate. There is a fairly minimal sequence variation in OspA among sensu strictos. However, there is more significant variation in the other two strains in Europe. So I think the protection there would be unknown, but more difficult to envision.

MODLIN: Thank you. One final comment.

PIETRUSKO: Bob Pietrusko from SmithKline Beecham. I'll also add that we're evaluating that and putting together a plan for a vaccine for Europe.

MODLIN: Thank you.

SNIDER: I assume we have no one from Connaught?

MODLIN: Well, we do, but I'm not. . .

SNIDER: Who?

MODLIN: I don't think there are any specific questions on the floor that that's the issue. There are people. . .

SNIDER: Who cares to respond to. . .

MODLIN: I'm sorry, Fred. Yeah.

RUBEN: I was going to say we're certainly here, but I don't really have this information. I don't know the answer to the question. Anything that we can help with, we're absolutely delighted to do so.

MODLIN: You bet. Thank you. Dave, shall we continue on?

HAYES: Good morning. Can everybody hear me? I'm Ned Hayes of the Lyme Disease Program at Centers for Disease Control in Fort Collins, Colorado. What I'm going to do is spend a few moments presenting to you the geographical distribution of risk of Lyme disease because in

thinking about the recommendations for use of the vaccine, I think it's important for the Committee and it's been important for the working group to address the issue of risk as Dr. Fleming mentioned. The principal component of that risk initially is the geographical distribution of the disease. Then I'm going to go on from there and discuss a little bit about how we've been thinking about the determinants for the decision of whether or not to administer Lyme disease vaccine and focusing in on some general issues that I've referenced specifically to Lyme disease for the Committee to consider.

From 1992 through 1996, well over 50,000 cases of Lyme disease were reported to CDC through the Net System. These were reported from over 1,480 counties, but 90 percent of those cases were reported from the top tenth percentile of the country distribution, so from about 148 counties. Those counties are shown here in red. This illustrates the focal nature of the disease. The majority of endemic activity occurs, as most of you are aware, in the northeast and in the upper north central parts of the country. This correlates pretty well with the distribution of infected vector ticks. This map, which some of you may have seen, shows the distribution of both *Ixodes scapularis* and *Ixodes pacificus* ticks. *Ixodes scapularis* is shown in red and blue and *ixodes pacificus* in green and yellow. The different colors represent whether the tick is reported as established from a county or simply reported. That reflects whether reports of the presence of the tick have demonstrated more than one life cycle of the tick or more than six ticks collected in a sample. That would define a county as having established tick population, and really reflects those counties where we think enzootic cycles really exists. Then reported counties are whether there've been some anecdotal finding—not anecdotal but documented finding of the tick, but not in sufficient numbers or life cycles to really give us the impression that an enzootic cycle is really prevalent.

Now the important component to recognize in relation to the other map of the surveillance data that I showed you is that the southern tick populations ecologically, we think, are different from the northern tick populations. That's based on findings that the infection rates are quite a lot lower. The indication with that may be a result of the feeding host—the host that the ticks feed on in the southern populations—which are primarily reptiles and lizards, as opposed to in the northern populations where they feed on primarily white-footed mice and other mammalian rodents. The white-footed mouse serves as a good reservoir for the *Borrelia burgdorferi*, whereas, the lizard does not. So with some help from Derlin Fisch and Carrie Fischer at Yale, we've been trying to use both the ecological and human surveillance data to improve our assessment of the risk of Lyme disease across the country. This is the initial step that Dr. Fisch took, which is to take that tick map that I just showed you and use a smoothing technique to sort of try to fill

in counties where we may not have data simply because people have not collected ticks.

He's then combined that with some information on the prevalence of reptile hosts out of the total number of potential hosts that the tick could feed on. This map shows the proportion of reptile hosts out of that total number of hots, moving from high concentrations in the southern tip of the Gulf states and then gradually becoming to lower proportions as you move northward. So when you combine those two sets of data, it can give you an indication of what is hard to measure ecologically simply because of a limit of manpower, which is the infection rates in the tick populations. Then combining the infection rates and the tick populations or the surrogate of the infection rates in the tick populations with a tick distribution in the human case data, he has recently generated—I apologize if any of you are red/green color blind; I'd be happy to show it to you later in detail—but again, showing the concentration of risk to be primarily up in the northeast and north central parts of the country with lower risk surrounding those areas, and then even lower risk in areas where we know the tick exists, but infection rates are low, and then virtually no risk in this sort of—we call it the "donut hole" of risk—and then of course the western—large areas of the western part of the country—western central part of the country.

Now we thought it would be helpful, in terms of the issue of deciding risk categories for use of the vaccine, to look at that at a state level. So this is, again, sort of a work-in-progress, but this is our initial assessment of the risk by state across the country, which you may want to keep in mind as you think about the actual wording of the recommendations and how it fits in with the geography of the disease. These would be the high risk states: Connecticut, Delaware, Maryland, New Jersey, New York, Pennsylvania, Wisconsin and Rhode Island. Moderate risk states, again, on our initial assessment would be Maine, Massachusetts, Minnesota, New Hampshire and Vermont. The low risk states is a fairly long list: Alabama, Arizona, Arkansas, California, District of Columbia, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan, Mississippi, Missouri, Ohio, Oklahoma, Oregon, South Carolina, Tennessee, Texas, Utah, Virginia, Washington and West Virginia.
These are states which we think really the risk of Lyme disease is quite low. Lyme disease vaccine may be indicated only for certain individuals engaged in particularly high-risk activities. States with absolutely no risk of Lyme disease based on ecological data would be Alaska, Colorado, Hawaii, Idaho, Montana, Nebraska, Nevada, New Mexico, North Dakota, South Dakota and Wyoming. Does anybody have any question about the geographical distribution of Lyme disease? Yeah?

MODLIN: Chinh, then we'll go around.

LE: I guess I raised this question at the working group, but maybe just for the rest of the audience to hear. I guess the Lyme disease surveillance has been around maybe in the last several years, maybe five—I mean, relatively passive surveillance in some states and active surveillance in a few areas where there are pilot studies from the CDC and so on. If we were to rely on a vaccine recommendation on surveillance data, how good is the reporting: over-diagnosis, over-reporting, under-diagnosis, under-reporting? I think that's one of the issues. I know as a practicing physician in California, we do have a lot of over-diagnosis. The second question I have is when you look at California, the reptile map surprises me a little bit because I thought that in California, we have a much wider distribution of reptiles and the reptile ratio is much more especially in, you know, Death Valley and so on. I mean, it's hard to believe that you can get disease from Death Valley down there.

HAYES: Again, let me answer the second question first because I don't know the answer to it. That's data from Derlin Fisch, so we'd have to talk to him about how California fits into that algorithm. It's only based— it's not a map of the risk of Lyme disease; that is a map of a percent of reptiles out of the total number of hosts. I think it's based on, you know, historic ecological data. So there may be pockets where you have a high proportion of reptiles out of the total number of hosts in California. I imagine that based on his data if you look at the state as a whole and that area as a whole, that you would find that there's a larger proportion of mammalian hosts for the tick than you'd find reptiles as compared to the southern/eastern part of the country. To get further clarification on that, you'd have to talk to him.

The question about the surveillance data, CDC started surveillance in 1982. It was in 1990 that a national case definition was developed. In 1991, CSTE made Lyme disease a reportable disease across the country. The data that I presented here is from 1992 through 1996. We feel that over that period of time, it's pretty solid in interpreting general trends and geographical distribution. There was a couple of states—well, really only Pennsylvania that I can think of—in 1992 and 1993 that didn't report by county. So the county data was missing for those two years from Pennsylvania, but other states did report. Through 1994 through 1996 particularly, I think the case reporting has been relatively standard. Now the active surveillance has been implemented in some hyperendemic states. Particularly, Connecticut has had a very active case finding system and parts of New Jersey. So that does influence reporting.

Studies in Connecticut and Maryland in the early 1990s suggested that in those highly endemic areas, anywhere from 10 to 16 percent of total numbers of cases were reported. Now we think that the majority of

those under-reported cases are uncomplicated cases of erythema migrans, which are the most likely to go unreported. There is substantial under-reporting in endemic areas. We also agree with you that we have suggestions that there's large number of misdiagnosis in non-endemic areas. So there is both over- and under-reporting. The under-reporting tends to occur in areas with the greatest numbers of Lyme disease cases and the over-reporting in the less endemic areas. Again, I think the data is certainly useful in terms of describing trends and in looking at the overall geographical distribution of the disease. I showed you a map of the top tenth percentile of reporting counties rather than showing you all the counties that reported Lyme disease during that period because you see a huge number of counties reporting a few numbers of cases, which we are virtually certain are either acquired in other counties or are not Lyme disease.

MODLIN: Marie?

GRIFFIN: Yeah. I think it's real useful to have a breakdown as far as especially the no-risk states. I wonder if the state is the appropriate unit when there's such differences within states, such as California and Pennsylvania, where it's really not very useful to have California classified as a low-risk state when there are a few counties that are very high-risk, like Humboldt or up in the northern area.

HAYES: That's a very good point. We've been wrestling with that on the working group and we appreciate your input on that in terms of trying to figure out how to formulate the document as it goes forward. We sort of had initial plans to present it, perhaps both ways; to have a map that describes the geographical distribution of risk. Then rather than having a list of 1,480 or 3,000 counties, perhaps just having a list of states because we thought that might be more useful to the practitioner. California is interesting from that standpoint. The state really as a whole is a low-risk state, but you're pointing out—and Massachusetts is another example where you could argue maybe Massachusetts should be a high-risk state. It has Nantucket County as the highest reported endemicity in the country. The cases of Lyme disease are concentrated on the eastern shore of Massachusetts. In western Massachusetts, we don't see reported cases of Lyme disease. So the state as a whole, we felt, should really be in the moderate category. These things are things that are in evolution and so we'll be thinking some more about that.

MODLIN: Thanks. Rich?

CLOVER: Did you show a slide that showed the distribution of ticks known to be infected with the organisms?

HAYES: No. That data really isn't available. If you think about it, you'd have to be going and doing infection rate studies in large parts of the country and it just hasn't— the resources haven't been there to do that.

CLOVER: Well, I guess I've then got some significant concerns about the methodology you employed. Obviously, in low-risk or no-risk states, the positive risk value of any case definition that you have, the positive risk values would be quite low. So I have some concerns about you even calling low to moderate risk the southern belt if you don't have some mechanism where you can confirm the organism is actually present.

HAYES: Oh, the organism is present. I mean, both the tick has been found and *Borrelia burgdorferi* has been found in ticks in the southeastern part of the United States. The infection rates where they have been studied tend to be about 1 percent. The problem really is in developing a national map that shows every county or tries to interpret or predict what the risk will be in every county with data that's only in several focal localities where it's actually been assessed. So that's the problem basically that we've been wrestling with Dr. Fisch. The best surrogate that we've come up with at this point, we're actually looking into trying to use some satellite data as well to come up with ecological correlates of whether the tick should be there and what the infection rates could be. This is an initial step of just looking at this relationship between reptile densities and the supposed ecological correlation with infection rates. So it's kind of—I agree with you; it's not perfect by any means. It's sort of the best we're able to do at this particular juncture.

MODLIN: Thank you. Further questions? Fernando?

GUERRA: I guess I'd be interested in knowing, and it's probably too early to know, but rather or not the listing of states and the different categories has changed over time: no risk, low risk, intermediate?

HAYES: Yeah. Well, this is pretty much the first time we've made this type of an assessment, but the disease has spread from its initial description in the 1970s. Over the last few years, we've tried several ways to look at geographical spread based on surveillance data. Over the time period from 1992 through 1996, which was when we have most confidence in the surveillance data, there really hasn't been a lot of indication that there's been significant change in the contiguous spread of the disease from the counties where it's previously described as hyperendemic. The incidence is increasing in the country, but the majority of the increase occurs in counties which are already known to be endemic. So there's some work that's been done by a group up at Maine Medical Center that's looked at spread of the ticks. There seems to be some spread up river banks in the northeast. There is some feeling that there may be some spread from counties to adjacent counties in Connecticut.

So there's some indication of it, but if you look at it on a national scale, the areas that have been classically described as hyperendemic have sort of remained that way. The areas of low risk have kind of remained low risk.

GUERRA: Is there any correlation with the spread of Rocky Mountain spotted fever?

HAYES: I can't answer that question. Yeah?

NEIL: Dr. David Neil; I'm from Merck. Is there evidence on the national map where you show the distribution of ticks that all these ticks from the different states of different demonstrated incidence of Lyme disease are of the same species or is this a species complex? A related question is has the vector competence of all the different states, you know—the high incidence states that have ticks and the low incidence states—been demonstrated to be equivalent?

HAYES: Yeah. That's sort of a historic argument that occurred in the early 1990s and is felt to be resolved. We think it's the same species of tick in the north and the south. The tick on the west is different; it's *Ixodes pacificus*. In the east and the northeastern part of the country, it's *Ixodes scapularis*. The tick has different feeding habits, as I described, primarily because of the presence of the reptile host in the southeastern part of the United States.

NEIL: Are they vector competent?

HAYES: Sorry?

NEIL: Are they vector competent?

HAYES: Yeah. *Ixodes scapularis* is a highly competent vector; other species of ticks are not. The Lone Star tick is not a competent vector.

NEIL: These are—within these species, are they combinations or are they totally different species?

HAYES: They're felt to be two—they're felt to be the same species, okay. I'm not, you know—I'm not sure whether, I can't really comment past that. I don't know the answer to your question.

MODLIN: Rich?

CLOVER: One brief follow-up question. You said that you know for sure that the organism is present in the south. How?

HAYES: There's been studies that have collected ticks and looked at infection rates in ticks, yeah.

MODLIN: Okay. Thank you very much, Dr. Hayes. I think that's it. I beg your pardon?

FLEMING: Do you plan on mentioning occupation?

HAYES: Sorry?

FLEMING: Were you planning on now going on talking about. . .

HAYES: I was going to go through the determinants and the decision to administer Lyme disease vaccine, yeah. I'm not going to actually talk about occupation specifically. What I've done, we tried to—in working with the working group—we've tried to develop what we thought were the determinants of whether, either on a Committee level or on an individual clinician level, one would want to administer Lyme disease vaccine. As Dr. Fleming initially pointed out, the primary consideration would be the risk of the disease. I've tried to put this into a little bit of perspective for the Committee, but the reported incidence in 1996 was 6.2 per 100,000. Varicella had an estimated average annual incidence of 1,498 per 100,000. Hepatitis A had a reported incidence of 10.3 per 100,000 in 1994. Again, as has been pointed out, there's a difference between, you know, reported incidence and estimated incidence, which was higher and would be for Lyme disease as well.

Again, the highest state rates: Connecticut, Rhode Island, New York —Connecticut with 94.8 per 100,000, and Rhode Island and New York as you see here. The highest county rate was in Nantucket, as I described, at over 1,000 per 100,000. If you look at the rates in the northeast and mid-Atlantic states, the average is 28 per 100,000. All other states including the north central part of the United States would give an average rate of .97 per 100,000. Now another consideration in deciding whether to administer the vaccine is the severity of the disease. Lyme disease is generally mild. If it's undetected and untreated, it may progress to cause debilitating symptoms, but it's rarely if ever fatal. The incidence of late stage disease leading to disability is unknown, but it appears to be uncommon and decreasing in frequency. That's based on the fact that we have some studies. NIH has a trial going on to look at chronic Lyme disease. They've been having difficulty enrolling patients.

It's a highly curable disease. Approximately 80 to 90 percent of Lyme disease cases present with erythema migrans. If it's treated in the early stages with oral amoxicillin or doxycycline, the overwhelming majority of cases will be completely cured. If this disease is diagnosed in its late

stages, it may require six weeks of IV ceftriaxone. Another component is the public health impact as Dr. Dennis mentioned in his introduction. Humans are the end-stage host. Thus, Lyme disease vaccine protects only the individual who is vaccinated and wouldn't be expected to affect the reservoir of infection. Are there alternatives to vaccination from an individual, secondary prevention standpoint? Is the early diagnosis in treatment of cases? From a community standpoint, there are also—also from an individual standpoint, thee are personal protection measures which have been advocated as sort of the cornerstone of public health policy up to now. That involves, you know, the use of repellant, and tucking your pants into your socks and checking yourself regularly after exposure to tick habitat.

Interestingly, several case control studies have looked at this and have actually failed to show the effectiveness. We think it's because people aren't able to practice these measures regularly enough to actually reduce their risk of the disease. Then there's also interventions to reduce vector tick density in endemic areas. These have been shown to be highly effective in limited circumstances, but have been not widely applied in sufficient degree to actually reduce the nationwide incidence of the disease. Finally, the last component we thought would be characteristics of the vaccine—and you've already presentations on safety and efficacy—and Dr. Dennis will now present some data on the cost effectiveness.

DENNIS: We've had at least one presentation before, I think, from Martin Meltzer. I may have mentioned it earlier about studies that we have been doing over time to look at the cost and benefits of vaccination against Lyme disease from a societal standpoint. We initially looked at a truly cost benefit analysis and submitted that for publication, and were told that the practicing physician community in particular was more comfortable in looking at it as cost of case averted and cost of sequelae averted in doing a more traditional cost effectiveness. So we have now reformatted that and presented that for publication in that form. I'm just going to very briefly describe some of the results of that modeling.

This model, as I said, examines the societal cost and economic benefits of vaccination against Lyme disease. It's based on a decision tree that evaluates the impact of six key components of cost vaccination. We don't know what the costs are, both of the product or how it will be administered for administration costs. We have tried to make estimates in range of that, including indirect costs to the person receiving the vaccine: in lost time, in transport, and work and that type of thing. The annual probability of contracting Lyme disease of an individual in a community setting is what we used. Again, it can be applied to an individual whose risk may be primarily dependent— not on a community or residence—but because of occupation or whatever. We looked at a

range of attacks rates, annual probability of getting Lyme disease from 5 per 100,000, which is just about as high as we see in reported Lyme disease cases by county. For instance, I think there are only about ten or so counties that report 500 cases per 100,000 per year or greater. Nantucket has exceeded 1,000 per 100,000.

So these are all clustered in the upper northeast. These are highly endemic counties. Again, they don't consider the under-reporting, but there is a large sensitivity analysis to account for a range. The effectiveness of the vaccine—and we looked at an effectiveness anywhere from 70 percent to 100 percent. That seems to be covering the range of the protection that would be offered based on the Phase III studies. The probability of identifying and treating early cases of Lyme disease—and this turned out to be quite interesting as having a major impact on the model. If cases of Lyme disease are identified and treated early, there's a great reduction in cost because of reduced morbidity from the disease. The next was the probability of sequelae of Lyme disease. Looking at three late stage rather costly sequelae of cardiac involvement, late stage neurologic involvement or late stage rheumatologic involvement with arthritis, and again, we also looked at the cost incurred for an early case of Lyme disease that was successfully resolved with treatment. Yeah.

So that's the basics of the model. I'll just show you the decision tree. So we had two groups—two arms here: sequels residing in endemic communities at a probability of acquiring infection of 5 per 100,000 to as high as—excuse me; I didn't say the other range that we looked at was 1 per 100, which would be quite a high community in a highly endemic area—to as high as 3 per 100 per year, which is the highest it's every been reported from special studies in communities that really were experiencing an outbreak of Lyme disease. So those were the three ranges of probabilities of acquiring Lyme disease. Then we looked at, of course, one arm in which the population was vaccinated; another arm in which the population was not vaccinated—looking at the probability of Lyme disease in these two populations and looking at the efficacy of the vaccine, as I said, from a range of 70 to 100 percent in our model.

Then going on to see those persons who did develop Lyme disease in the vaccinated group; whether or not it was recognized and treated appropriately in the early stage—yes or no—and then what the probabilities of the sequelae of either having complications of disease or case resolved in these two arms were. Similarly, looking at the same probabilities in persons who were not vaccinated, and of course, looking—bracketing it by the costs of the vaccine and the costs of the sequelae. I'm just going to show you one graph which incorporates all those elements in the model, but looks specifically at three things: the probability of acquiring Lyme disease, the risk to the person being

vaccinated, and the efficacy of the vaccine. Here in this cost effectiveness model, it expresses effectiveness of the vaccine ranging from 70 to 100 percent and then the cost of the vaccination per year. We looked at this as a one-time shot of what the cost benefits would be to an annual cost—a single annual cost of either $50, $100 or $200.

Then, as well, looking at the cost per case averted in thousands of dollars and the cost per sequelae averted in thousands of dollars. The important thing to look at I think is this line right here. That's where the cost to society equal the benefits at this society. This is the 0 line here. You can see that when the probability of Lyme disease of an individual or community is 5 per 100,000, at none of the ranges of probability that we looked at would society benefit for either vaccinating that individual or vaccinating all the persons in that community. At a probability of Lyme disease of 1 per 100 per year, you can see that at the least cost of the vaccine, that there is—does meet the threshold of a cost benefit to society for the least cost. It does not for the greater cost, but it at least approaches it for the $100 cost. If you look at the individual or community risk, at the very highest level we would think would be happening in hyperendemic areas, you can see that at any of those costs, the vaccine—its society— comes out equal on the cost or benefits of the individual gain or the community being vaccinated. Are there questions about that?

MODLIN: Questions for Dr. Dennis? Yes, Dr. McKinney.

MCKINNEY: I've been unclear about the time frame of your analysis. Was this a single year that you looked at or are you considering the possibility of a potential for many years at a time? If so, you're using only an annual incidence rate for repeated exposure to the organism.

DENNIS: It looked at the costs for complications of illness out, I believe, eight to ten years. It looked at the cost of the immunization as being a one-time event.

MODLIN: Chinh?

LE: I think this is a disease where cost effectiveness studies are very, very difficult to conduct in the real world as you know. You probably used some of the standard treatment recommendations to put in your figures, you know: doxycycline, 21 days; amoxicillin and ceftriaxone, four weeks and so on. In the "real world," unfortunately, a lot of patients are getting antibiotics right and left for years, and years and years for presumed Lyme disease. A lot of people are getting antibiotics for tick bites, which are not recommended. So those are very fluctuant; those are somewhat kind of provider-specific and sometimes just county-

specific because of the fear of Lyme disease. So it's very hard to generalize cost effectiveness on a national scale.

The other issue I want to—beyond that is when we make a recommendation for this disease, despite the fact that our policy is that we have to make any recommendation with some kind of cost analysis, this vaccine is going to be, unfortunately, manufacturer-driven and consumer-driven for most of the areas in the country. I say that because as Dr. Katz pointed out, it's a "yuppie" disease. I would not dare to say that where I live because people will put more ticks in my house. I know there's a very active Lyme disease group. Unfortunately, this is going to hit the providers, meaning the private practitioner, a lot more than the public health clinic. People who will pay a lot of money for their Nikes and their Esprit and shop at L.L. Bean's will have no consideration for cost effectiveness when they want a vaccine because they're going to travel to Cape Cod.

On the other hand, it's the migrant workers who put cheap grapes on our table who don't get access to this vaccine. It's one of those big ethical dilemmas for this vaccine. So I think when we make the recommendation for this vaccine, I think—I don't think that we should emphasize cost effectiveness as much as how to put this vaccine in the right perspective—put the right perspective of risk perception and try to perhaps offer to the providers some answers for patients who request Lyme disease vaccine who don't need it. For example, emphasize the limitation of the data and the limitation of what we know about safety and duration of protection. I think putting some ways for providers to resist demand of this vaccine is more important than trying to build cost effectiveness.

DENNIS: I think Dr. Chinh Le has raised some very important questions, particularly about the modeling—yes. We just took that model in a very pure sense and didn't look at the impact of vaccine on a lot of other either human—I mean, the public's actions and the public's response to having a vaccine available. As you say, the costs of Lyme disease are extraordinary in this country. Tens of millions of dollars of year are spent on diagnosis. Most of that is spent on diagnosis that is not rationally conceived as there being a need for that serologic test being given. As well, there is enormous cost with treatment of Lyme disease and much of it is perhaps unnecessary treatment of Lyme disease. We don't know what the impact of having a vaccine available will do on patterns, either physician patterns or public patterns, of having to do with diagnosis and treatment of what is perceived as Lyme disease. So we, of course, plan to have a continuing strong education program. We've got right now a number of programs with professional bodies—such as the American College of Physicians and the American Nursing Association—to try to guide not only the care community, but

also the public into a rational approach to diagnosis and treatment of Lyme disease. That will have to continue obviously. Any other questions? Yeah. Any other questions?

MODLIN: Chuck?

HELMS: Sort of following up on what Chinh just asked. Is there a way of looking at the cost effectiveness from a more distal perspective than, if you will, national—the way you looked at it here; for example, working with folks in the states or working with health care delivery systems in highly affected states to determine whether this thing will be cost effective?

DENNIS: Well, Dr. Ned Hayes in our group has been working with a number of people in the field to try to look at prevention effectiveness of various strategies to reduce the incidence of Lyme disease, both individually for comparative purposes, but also to see if you include more than one prevention tool in your effort to reduce Lyme disease in a community. We don't have any data to publish on that, but there are models that we've been applying, and that based on data of various degrees of soundness, that we are trying to validate with ground truthing studies. We would actually hope to, within the next several years, put this prevention effectiveness at the community level into actual— implement it and then measure the impact of these various interventions, singularly and in a combination.

MODLIN: Georges?

PETER: A related question—of course, the term "yuppie" has been bandied around and poor Dr. Katz regrets that he ever used the term, I'm sure. My impression living in an area where Lyme disease is endemic—and I'm from Rhode Island—is the impression that this is not a disease that affects the lower socioeconomic groups. It's very region-specific, even within a small state like Rhode Island. In your case reporting, do you collect socioeconomic data? For example, like Chinh mentioned migrant farm workers. Well, there are not a lot of migrant farm workers on Nantucket. So, you know, my question is I wondered do you have any data on this?

DENNIS: Obviously, the tick doesn't select its host based on its financial. . .

PETER: No, but the point is. . .

DENNIS: But it is true that this is a rural disease.

PETER: Right.

DENNIS: And it's a disease especially of suburban communities that are living on large property lots. So it does probably, although we've never that I know of ever looked at the socioeconomic level of people that are impacted by Lyme disease. It probably does reach the middle and upper middle class especially because of that living situation, but you just can't broadcast that either because anyone who goes out into a tick-infested environment or environment infested by the ticks that transmit the Lyme disease infection are at risk. For instance, in those communities that are suburban that at high risk in New York and Connecticut, occupational groups such as landscapers are particularly at high risk. Linesmen perhaps are at high risk; people who clear brush we would expect to be at high risk. So it's not just people who are at high socioeconomic levels. It's obviously also anybody who recreates or does leisure activities in tick-infested areas. This includes parks.

PETER: You know, I've never seen a case from a child of inner city providence unless they happen to go to the Boy Scout camp which is down by Westerly so indeed, that bears out your point. Still, what a person does is as important as where they live?

DENNIS: Very much so and I think we'll touch on that a little bit later.

PETER: The other issue is, of course, Nantucket is the highest risk area and that includes like—I mean, that basically is the population that lives there. Once you publicize that Nantucket's the high risk area, there's a market that's going to develop for those who travel, which many people do in the summer to Nantucket and Block Island; yet, the risk would be very specific. If you're cruising in Block Island, you're not going to be at risk unless you happen to take a hike through the woods. Those kind of elements will need to be addressed in giving providers guidance in who should really get the vaccine.

MODLIN: Right. One more question and then we do need to move on because there's a lot to cover yet. Fernando?

GUERRA: I couldn't have stated the case more eloquently than Chinh. I suspect that some of it relates to perception and to perhaps not really being so oriented to establishing or even considering a diagnosis like Lyme disease in those individuals that perhaps are from other parts of the country and/or have different colors or languages, et cetera, because the symptoms at times are very vague. I just wonder if maybe as one tries to gather additional information, it might be possible to perhaps call attention to this as one of the occupationally-related conditions that may be is misdiagnosed or not even thought about it within the network of migrant health centers? The Migrant Physicians Network would be a very good, I think, place to perhaps provide some of the information

about this and to maybe initiate some reporting to see if, in fact, those populations might be affected by it.

DENNIS: That's a very good idea. I would think that there may be considerable migrant populations, agricultural workers in Maryland and Pennsylvania that could be putting themselves at risk.

SNIDER: And New Jersey. Just to elaborate a little bit more on that point, I think probably the general discussion is correct, but there's also another factor which hasn't been mentioned, which is the level at which people elect to seek medical care. I think all of us who've worked in inner city hospitals know that the tendency is if a person's got diabetes, if they're lower socioeconomic groups, they're more likely to show up in ketoacidosis rather than with the frequency of urination. So there's also that aspect of it too; that it may be that some groups would have Lyme disease but not necessarily—because of the mild nature, much of the disease never seeks medical care for it.

MODLIN: I appreciate it, absolutely. Thanks, Dixie.

FLEMING: Prior to engaging in the general discussion, we did want to give an opportunity for some limited public comment as we talked about at the early part of the meeting. So Mr. Weld?

WELD: Good morning. I'm David Weld, Executive Director of the American Lyme Disease Foundation. One thing I think, if this heat keeps up, the ticks won't have a chance around here and Lyme disease will be a moot issue. I've been listening very intently this morning. Lyme disease, especially in the northeast and the upper midwest, has already threatened or impaired the health of at least 100,000 people and has affected the quality of life of tens of millions more. I want to touch on this quality of life issue a little bit. I live in Westchester County. I'm glad to see somebody else who is here today from a highly endemic county. I'm not kidding you; every single person I know in north Westchester is afraid to go outside. I know people who've paved over their backyards so their kids will have a chance to play without the fear of being bitten by a tick. People have put decks around their house so they don't have to walk on the ground again, and it goes on and on.

Some of this, obviously, is a little bit ridiculous, but I currently—and I live, you know, with a couple of acres—employ every method I know to reduce the incidence of ticks on my property, including spraying once a year, mowing the lawn, using a totally integrated approach to reduce our exposure. Nevertheless, my eight-year old son—well-trained no doubt—took two ticks out of his scalp this past winter. In the northeast, as many of you, we had a very mild winter and the adult ticks were out just about year-round this year. We do feel that the vaccine shows

great promise as an important new preventive tool. We will do all we can to educate the public and medical community about its availability and use.

We get between, right now, 200 and 250 phone calls a day into the office, plus another 100 letters a day requesting information. A lot of them want to know about the vaccine; a lot of them come from areas where ticks are not in abundance; others come from areas which are highly endemic. I just want to once more get back to this quality of life issue. There are an awful lot of people out there who are afraid. There are six or eight children in my community right now that I know of walking around with IV shunts in their arms because they've been diagnosed with Lyme disease. In a couple of cases, I don't think they have it. When a children's vaccine becomes available, it may be very beneficial in that it's going to reduce the incidence of a lot of people claiming to have Lyme disease when they don't. We look forward to it. Its use along with everything else will help eventually to reduce the rising trend that is characterized of reported cases of this disease since its discovery 23 years ago. Thank you.

MODLIN: Thanks, Mr. Weld.

FLEMING: Thank you very much for those important, very important comments. We do want to move now to a general discussion. One very quick item that we wanted to cover before that though was just to explain a bit more the issue around risk. You heard a discussion around geographic risk, but I think Dave wanted to put up one overhead that talked about risks related to other factors as well that we would, as a working group, intend to incorporate into whatever final statement on risk that we had.

PARENTI: Thanks. I'll just try and make this quick. I think there's no question that environmental risk is the key to assessment of whether a person can benefit from vaccine or not. We've done our best over the past several years to try to develop a mapping technique that will give care providers and the public a better idea of risk. We know that there are lots of caveats to these mapping projects. As Ned mentioned, it's in process and we actually have a national working group to best be able to show what the geographic basis and ecologic correlates of risk are. However, risk in Lyme disease is really an individual concern. I just want to lay this out because I think we always have to think that a determination of the risk should be made on an individual basis.

The individual risk is based on a person's susceptibility to bites by infected tick vectors of *Borrelia burgdorferi*. The level of risk is a function of the density of tick vectors in the environment, which varies very much by place-to-place and by season; the infection prevalence in the vector ticks; and by the degree of persons the ticks contact, which is obviously related to the type and the duration of a person's activities in

a tick-infested environment. High risk activities are those which involve contact with foliage or ground cover and habitats favorable to deer and to rodent hosts of Lyme disease bearing ticks. Individuals may, even in high endemic areas, reduce their risk of Lyme disease by avoidance of tick-infested habitat; when in a tick-infested habitat, by applying personal protective measures to protect against these ticks, such as wearing protective clothing, using repellents and regularly checking for and removing attached ticks to skin or clothing. We know that if you remove a tick before it's been attached for 36 hours, you've probably interrupted any transmission.

Further morbidity and cost from Lyme disease can be significantly reduced by detecting and treating Lyme disease in its early stages. Such early and correct treatment almost always results in a prompt and uncomplicated cure. So I'd like to remind you that persons who reside and work and participate, or recreate and have leisure activities in and travel to areas of high or moderate level of risk may, because of the factors that I've listed above, be at no or low risk for Lyme disease. Similarly, people who live in areas that we've categorized as moderate risk may be, because of their focal geographic risk in a county or in a township and because of their activities that expose them to ticks in the environment, may be at high risk even though they're in a generalized area that we consider to be a moderate risk. So it has to be really an individual assessment.

FLEMING: We'd now like to open it up to some general discussion and some general feedback to the working group on the proposed framework. Just to make two very small points. The risk levels that we're talking about, talking about potentially three. I don't think a final determination has been made on that, but that clearly is risk for the individual, as Dave was just saying, of which risk by state or county needs to be incorporated. We're talking about individual level risk. Then the issues around cost effectiveness, I think have been discussed briefly. I just wanted to make the point that we're talking about some very loose thresholds based on cost effectiveness. Some of the ambiguities around cost effectiveness for Lyme disease are to a certain extent mitigated by the fact that we're dealing about a disease whose risks varies by orders and orders of magnitude across the country.

So for example, the cost effectiveness analysis that I reported only went down to the national median, but in many parts of the country, in those areas, we're talking about incidences in the less than 1 per 100,000 range. When you start thinking about the cost of vaccine that would be needed to prevent a case in those areas, you do get—I think all of us get to some point in which we might say would no longer be cost effective. So again, not an absolute cost savings or absolute cost effectiveness, but wondering whether or not general issues around cost

effectiveness, given the grant span of risk, are appropriate. So I'd like to open the discussion to comments that the Committee would have about any of the aspects that are on the proposed framework, recognizing that that's what it is; it's proposed and will undergo evolution.

MODLIN: Chinh?

LE: The transparency that you showed up there, Dr. Dennis, I think the text is very good and I don't see it in this original draft. Do you plan to include that in this draft, you know, the personal risk or whatever? I think that puts it very clearly for the providers and the "customers" of a vaccine to really look at what their risk is.

DENNIS: Actually, we've tried very hard to get some sort of draft in your hands with a very short time period for this meeting because we know that it's quite possible, probable that a vaccine will be licensed some time in the next two to three months, and that we would like to be able to have pretty strong consensus on things at the October meeting. We did distribute a draft to the ACIP membership only that did not include some of the language that we now have in a subsequent draft. After this meeting, we'll develop a next draft and distribute that to you as quickly as possible that will incorporate this.

FLEMING: I think that is very good feedback. Thanks, Chinh.

LE: I guess the other question we discussed in the working group was whether we should list the occupations that are at high risk for this, you know, like the gardener and the people who work for Pacific Bell putting lines in and so on. I guess one of the discussions was maybe we shouldn't because if we put those occupations in text, would their employers be required to vaccinate? If they don't, will they be medically liable for this? So it's just a broad statement about occupation. I don't know whether people feel that it should be put in. If you put it in, in a sense, it is difficult just like hepatitis A where we don't, you know, make the employers give the hepatitis A vaccine. On the other hand, the other side of the argument—at least on a social/ political argument—is if you put it in, at least some of the people would not demand a vaccine because, you know, they are migrant workers who work in our fields and don't know about Lyme disease and so on. Their employers would have some kind of responsibility to cover this kind of medical cost for them. It's an ethical issue as well.

GUERRA: It could also open up an unbelievable Pandora's box because then, you know, you obviously have a lot of other related issues to exposure, and insecticides, pesticides, and sanitary field conditions and a lot of things that I think certainly should be addressed. I, like you, think that there

should be some way that we can communicate to those occupationally-related groups that may be are at risk and/or the employers without putting the burden that they should provide it because otherwise, I think that just opens up some very complex discussion. I wanted to ask Dr. Hardegree a question. In the FDA review of the different phases of the studies for licensure and for new vaccine products, is there some guideline or requirement for broadening the population groups that are studied in the incidence where there are groups that are at potential risk for a condition that one is trying to prevent?

HARDEGREE: If you're asking are there requirements to include particular occupations or particular populations in a segment, we do not have specific guidelines on that. What we do have is that we need to try to address the issues of gender that we—and increasingly, documents are being prepared about the need to address different segments of the population. FDA is increasingly concerned about lack of populations not being studied—for geriatrics; we recognize the issue in pediatric populations—and as you heard several times, took this to the Advisory Committee. What we do not have though, the ability to do, is to force the inclusion of ill people or other people into a study. You can raise it as a question. Dr. Susan Ellenberg has been very concerned and has made several public presentations about trying to get broader segments of populations included early on in various studies, but no; we do not have specific requirements other than the gender and addressing some of the minority issues. Those are new initiatives in many ways.

MODLIN: Let me ask the members of the Committee how they feel about the proposal regarding recommendations based on risk levels in terms of numbers of risk levels that Dave brought up earlier. We've sort of listed three up here as a starting point for purposes of discussion. I think this is the area in which you wanted to go on with this discussion, is it not, Dave? These risk levels can be determined. Then the second issue I think we really need to be focusing on is these risk levels are clearly going to be determined geographically. What should the geographic unit be? Should we be talking about specific either states or counties, or should we be talking about states or counties that have a certain minimum risk level as defined by surveillance?

I guess you've always got the third issue, which is if you ultimately define risk based on a certain minimum incidence of a disease as determined by surveillance, and you go in and you have a successful immunization program in that area, the incidence is going to drop at some point in time to below that level that you'd determine. All of a sudden, is that geographic area going to be bounced into a lower risk category as a result of surveillance, which is sort of done on an artificial basis as opposed to what the true risk actually is? So those are kind of the issues I think we need to be focusing on as a Committee. Mimi?

GLODE: As a non-invested person from a state that sees only imported Lyme disease, it looks very reasonable to me to have these three categories. My only issue is I look at these and look at other recommendations as, you know, if you're in the highest risk, then I just wonder if the statement shouldn't be "is recommended." So, you know, "should be considered" sounds to me less strong than "is recommended;" so "a rotavirus vaccine is recommended." I know in previous statements, we've used "is recommended." So I just didn't know if you deliberately wanted it to be less strong in the highest risk groups.

FLEMING: Our understanding, first off, of the package insert is that the language is going to be "should be considered." That's not to say that we have to follow that. Secondly though, I think that you've heard that there are many issues around this vaccine that make it a tough decision, I think, whether or not to explicitly say "is recommended" and in essence, remove a little bit of that patient/provider choice. Alternatively, a strong "should be considered" would recognize that ultimately, whatever we say about risk is going to be fuzzy and to allow a little bit more opportunity for physician/patient discretion. I think it was, therefore, consciously that we had said a little bit weaker than "is recommended," but rather "should be considered;" that's open for discussion.

SNIDER: Well, I think one of the things here, Dave, is that if you really are going to focus on the individual as opposed to the community or the county, then it becomes a situation where I think Mimi's comment about saying "is recommended" becomes more imperative. In other words, if you were talking about an individual who has the highest level of personal risk because of what they do, and because of where they live, the activities they engage in and so forth, the more imperative it becomes for an individual to, you know, consider doing that. So it becomes very problematic, I think, to take an individual approach, and break it down into just three groups and come out with something that is strong enough for some people in that highest level if you only have three, and yet, allows for the flexibility you're talking about, you know.

At extreme, if you talk about a person who is living in Nantucket, who is outside sixteen, you know, fourteen hours a day—whatever—with both occupational and recreational activities that put them at exposure in specific habitats, you know, or habitats for ticks, that becomes, you know, a situation if not recommended, certainly strongly considered. Whereas, you know, as people decrease the level of their risk behavior, the level of consideration becomes less. So I think it becomes difficult. I guess what I'm trying to say to get at a bottom line, it becomes difficult to take three risk levels, but then talk about individual risk. It's hard to collapse all the individual activities into three risk levels. It's easy to classify the country as we saw earlier—relatively easy to classify into

high, medium and low, but not necessarily individual behavior into high, medium and low.

FLEMING: That's a good comment; I appreciate it. Other comments on that? I think you hit it right on the head there, Dixie, in that the real question in that highest level is how far down to extend it. Many of the people that would fall into "highest level" actually have a fairly low absolute risk. So the question is—is there a subcategory of that highest level that really does warrant our recommendation? Yeah.

MODLIN: Marie?

GRIFFIN: I guess I would favor the "should be considered" because in the clinical trials, these are presumably high-risk people. The baseline risk is still about 1 per 1,000 per year, which is not that high. The efficacy is 50 percent, 70 percent; it's not complete. We don't know anything about long-term efficacy. So maybe we're recommending that they get a booster every year for a risk of 1 in 1,000. So I think that's a very personal choice. I mean, I think Nantucket's different, but that's very unusual. I mean, I would assume that people who participated in these trials consider themselves to be at fairly high risk and still we're only seeing 1 per 1,000 per year.

MODLIN: Stan?

PLOTKIN: I feel moved to make a general comment here; that is leaving aside the questions of safety and efficacy of individual vaccines and issues which clearly are important, but I'm somewhat surprised by the tenor of the conversation in a way in that clearly the direction of the conversation is to limit the use of a vaccine which has been shown, at least at this stage, to be safe and efficacious in contrast to other vaccines where we are continually trying to enlarge the recommendations. Now the second point is that this, somewhat like rotavirus vaccine—it harks back to prior discussion—is what I call a "vaccine of convenience," the first of many. That is to say these are vaccines where individuals are going to make choices about whether or not their risk is significant.

If and when there is a vaccine against chlamydiae pneumonia, for example, theoretically against the risk of atherosclerotic heart disease, the risk of any individual is going to be variable. Not only that, but his perception of his or her own risk is going to be variable. One is going to have to permit the individual to make some choices about whether a reduction from 2 in 1,000 to 1 in 1,000 is significant for that person. So I would urge the Committee to distinguish in this type of vaccine between public health issues and individual issues. It may well not be desirable for the State of Colorado to recommend Lyme disease vaccine for its inhabitants or to pay for it in distinction —let's say to

Connecticut—but that is the public health side of it. The individual side of it is a question of the choice of the provider and the patient himself it seems to me.

DENNIS: If I could just answer. . .

MODLIN: Sure.

DENNIS: . . .some questions that were raised by the last two speakers. First, I think that individuals that are living in highly endemic communities or counties in particular, I think that they should consider—I mean, they should start a dialogue amongst themselves in the family setting. They should start a dialogue with their care providers, a dialogue with what they can read from what they have been provided by the public health community; "Am I really at risk? If I live in Nantucket for three months of the year, am I at risk? I mean, do I live in a house that's out surrounded by a gorse in a tick-infested environment or am I living right down in a Nantucket town and just walking out to the boat dock?" So people who have been identified as either working, or living or recreating in these high-risk areas, based on what we know about the environmental risk of exposure to infested ticks, they need to start that dialogue so they should consider it.

SNIDER: Dave, in pace with what you've just said is that the risk level is based on the risk in the geographic area and not the individual risk.

DENNIS: Well, it has to start somewhere. If you're living in the Rocky Mountain states where there's absolutely no risk, people do not need to consider unless they're going to a high-risk area for one reason or another. I think it's useful to have more than just high risk. I think it's important also to have moderate risk to accommodate some other areas.

SNIDER: I'm not disagreeing with anything you've said. What I'm trying to do is clarify the presentation because, you know, when you put up your narrative, you talked about individual risk. Dave made a comment—Dave Fleming made a comment about that this is going to be based on perceptions of individual risk, which led me to think that when you have risk level up there on that overhead, that you're talking about individual risk. The way I hear you now, that risk level is a risk level that is based on geography.

DENNIS: Yeah. I think you have to marry the two.

SNIDER: Okay.

DENNIS: I mean, people have to. . .

SNIDER: Alright. That clarifies it more.

MODLIN: Okay. Barbara?

DEBUONO: Yeah. I'd like to make a couple of comments about this coming from a state and now in a state that has fairly high incidence for Lyme disease. I like the idea of developing the risk categories based on both geography, as well as individual time spent in that geography and the kind of time spent in that geography. I think Dave's comments are well taken. I think that high, medium, very low to zero—fine. In terms of the recommendation, "should be considered" versus "may be considered," I think "should be considered" is fine. I think that even going beyond that is okay too because I know that certainly in the New York area, we may very well go beyond the words "should be considered." We may say "for residents who reside in the eastern end of Long Island, living in the following circumstances, we recommend this." I'm comfortable with that.

I think one of the biggest problematic areas here, going back to the comments made earlier, are going to be what to do with children. There is going to be tremendous pressure once this statement comes out, once the license for vaccine is approved, the statement comes out, pediatricians, family doctors and families are going to have—there's going to be tremendous pressure to use this in children. So any statement we make about this ought to be real clear about our view on children; that either we are doing studies on children and can't make a recommendation until they're done, or that it can be used in children. I'm hearing thus far that it can't be. That's where there's going to be tremendous pressure because you'll have an adult in the family—two adults vaccinated and two or three children not vaccinated. It's going to create a lot of anxiety between practitioners and families.

MODLIN: Well, I think the issue there is going to be number four, which is the inclination not to diverge from the package insert in there. I think when we start to talk about pediatric issues, we're going to be very careful that we are cognizant of that issue. Yeah. Go ahead, Barbara.

DEBUONO: The final thing I wanted to say is that part of the, you know—while this is important, there's also this issue of who's going to pay for it. Sometimes when we make these recommendations of highest risk level—"we recommend it" or "should be considered"—the question comes up, who's going to pay for it? You know, I think with this vaccine, that's a little bit more moot for us at least because we don't feel—and I certainly don't feel as a Commissioner, somebody running the Medicaid program—any imperative to pay for this at this point. I certainly do feel that we should take a strong view about those people at highest risk in our community.

MODLIN: Fine. Neal, you've had your hand up for a long time.

HALSEY: I have a number of comments to make. First, I'll make a disclaimer or a potential or perceived conflict of interest, even though we're not required to. I am actively conducting studies on children in the eastern Maryland area as are several other investigators. Doing them, I've also participated serving on the Data and Sector Monitoring Board for the efficacy trial. First of all, I think in terms of the issue that was on the table for discussion over how one addresses the risk and how to do that, I think the problem is going to be even larger than just those in the geographic area. We have an enormous amount of mobility of people in and out of areas of increased risk, but we've already done this with several vaccines for travelers. I just pulled out the Red Book and looked at it.

We have a special section on immunization for foreign travel which we—and I think people will want to have a little bit more guidelines along the path that David Dennis was trying to take us in terms of what your activity is in the high-risk area and for how long that you're expected to be there. Certainly one of the high-risk activities are these Boy Scouts. They all seem to be—there are Boy Scout camps up and down the East Coast in the highest endemic area off on these islands in the eastern shore of Maryland. We are going to need to have very specific guidelines. With regard to the pediatric issue, our committee is drafting guidelines. We will encourage adherence with the package labeling, but we really do want to see the pediatric studies move forward as fast as possible. I will just tell you I would hope that that can be accomplished before next year's season based upon immunogenicity data if the FDA will agree with that.

Last, just to address the repeated comments, which I think are clearly overstated about this being a "yuppie" disease, the eastern shore of Maryland is far less well off than all of the eastern part of Massachusetts it seems like because we do have people in the lowest socioeconomic status who are living, residing and working in areas of marked, increased risk of Lyme disease. I think we do need to figure out the ethical problem that Chinh Le brought up. How are we going to have their vaccines paid for? It really will be another dilemma. Here's somebody in a high-risk area, and I share Barbara's point that I think should be administered. I mean, it should a stronger recommendation as indicated in those settings for people who are working out of doors, you know, for X— you can calculate whatever time you want to—in these high-risk areas or visiting them. I think it would be highly inappropriate for the vaccine not to be paid for in specific settings for some limited high-risk group in people who are in the lower socioeconomic status. That would just be wrong.

MODLIN: Okay. Rick Zimmerman.

ZIMMERMAN: The issue of this looking at both the geographic and the personal care habits or occupations reminds me of a two-stage sample in epidemiology. I'd encourage the working group to really perhaps think in those kind of clear terms; that really there's first the geographic look and then the second stage is personal risk. Clearly, even in the highest areas, we would not recommend vaccination of a 68-year old person in a nursing home; whereas, we would for perhaps in some of the highest risk, most everybody else. I think there is really a two-stage and I think we need that kind of clarity to guide practitioners.

MODLIN: Fernando?

GUERRA: In deference to Dr. Plotkin's point of earlier, I think that at the front end, we have to recognize that this is a public health consideration, especially in the instance in—and I don't think we can separate truly the individual side of it from the public health side of it. I think several times we've heard about the importance of quickly coming to some consensus around how we're going to protect children because that's going to be imminent once it is licensed and available. The second is the population that, again, we continue to be concerned about that do spend—and in looking at the risk assessment, a description. There's no question that seasonal or migrant farm workers spend extended periods of time under those very same conditions. When you look at the extended period of time that they spend in the mid-, central part of the country in the Michigan/Wisconsin area for the three or four months in which this is most prevalent, I think that we need to quickly move to gather some data about the instant rates of the condition.

MODLIN: Chinh?

LE: I just wanted to correct a perception if it was wrong, you know, listening to Dr. Plotkin. I really don't mean to say that I'm resisting the vaccine. Actually, I certainly welcome this vaccine. If I were on the East Coast, I would say exactly what Barbara said about, you know, a stronger recommendation. Again, since this disease is so different in a different part of the country where I come from, I would expect a lot of patients who're really at a very, very low risk, but a heightened fear for Lyme disease to request the vaccine. I think it's our job to lay out some kind of guideline for providers to say, "Look, you know, you may be at low risk. Although you want the vaccine, let's consider this—the limitation of the vaccine in terms of what we know about duration of protection and safety and so on." Perhaps at the very end of that paragraph say, "No, the vaccine should not be denied to anybody who request the vaccine even if they know the cost benefit of it." I guess we're not here to deny

people the vaccine if the fear is—if the risk is even low, but they wanted to. I guess the question is who is going to pay for it? I think the insurers' point of view also has to be in here somewhere for those low risks.

MODLIN: Are you comfortable with that opinion given the level of the safety data that we have at the moment, particularly in groups for which the vaccine has not been given in the clinical trials? In other words, is there any concern that at the moment, that someone that we would perceive at being extreme low risk who requests the vaccine, we don't take into account a perceived risk of adverse effects that we're unaware of? I guess what I'm trying to get at is I'm still concerned about the pediatric issue, and that is we know nothing about the safety of this vaccine in children yet. Should we be put in the position of even being in any way permissive with respect to. . .

LE: I'm sorry. What I meant is that anybody who requests the vaccine. . .

MODLIN: Right.

LE: . . .should not be denied. I'm not saying about the pediatric issue.

MODLIN: Okay. Fair enough.

LE: I'm talking about whatever is in the FDA, we're sure.

MODLIN: Okay.

LE: I'm talking more in terms of what Stan said; that we should deny the vaccine or resist the vaccine for people who want it.

MODLIN: Okay.

LE: But that's what I'm saying.

MODLIN: Just want to clarify that. John?

LIVENGOOD: Yeah. I guess one question I would have back is then would Kaiser cover that in their plan or should other insurers, or what will we do about those people who might request it and be unable to afford it? I mean, you've seen the range of estimates of cost. This leads a little bit into my second thing. Actually, under item 4—I don't know if you want to move on to other things—but I'm quite concerned about what the statement would say about boosters and the possible need for them. One interpretation—and it is one that I'm sort of prone to—is the difference in efficacy between the first year and second year appears to reflect some necessity for this vaccine to have a relatively high titre, perhaps

because of its novel way of working, which is to kill the organism in the tick itself. Considering that, I'm really concerned as to what the statement would say about possible need for boosters. I mean, we have certainly issued other statements without long-term experience in the U.S., but like with varicella or some of the others, we had years of observation in other countries. We're not going to have any other observations and very limited data, it sounds like to me, about subsequent seasons.

MODLIN: Okay. Carolyn?

HARDEGREE: I think as Dr. Elkins indicated, our Advisory Committee and particularly the experts that we brought in regarding Lyme disease were very concerned about moving forward with any recommendation of any statement at the time of approval that would address booster without having data regarding the safety. They did recognize the antibody data that they saw showing some decay and they saw the evidence the need for the third dose. So they were very insistent on having some booster data.

MODLIN: Georges?

PETER: Well, I think to reiterate the importance of children, I think that in order to fortify the physician who recognizes that the vaccine is not licensed initially for children, and yet the parent demands it, we're going to have to spell out all of the reasons why the vaccine might not be safe. In other words, we have to give them the arguments and the concerns about it having negative consequences over a long period of time. In order to prevent ingestion, you have to then give the reasons why a booster isn't yet indicated. It's not enough to say "data not available yet." We have to give what the theoretical concerns are.

The second point relates to the category of recommendations. I do think that we should consider a category of "is recommended." It really relates to the consideration that ultimately, this vaccine will be released in children. Neal pointed out the eastern shore of Maryland. Clearly, there are children who are VFC eligible who indeed probably do acquire Lyme disease. I don't think we have them in Rhode Island, but clearly other parts of the country do. So we'd like to make sure that those children do have access to the vaccine. I think we can—for a VFC recommendation, I think we have to say "is recommended." So developing that category now may have some implications ultimately for the use for providing funding for this vaccine.

MODLIN: Let me throw that back to John. In the discussions for the rotavirus vaccine, we had a slightly different take on that, which was we didn't feel necessarily that we had to have a fully recommended statement

that said the vaccine was fully recommended in order for it to be considered for VFC. Is that. . .

LIVENGOOD: Yeah. I had a long conversation with Kevin, who's not here; will be back later this afternoon. He's never supplied me with any draft language for the resolution for something less than is recommended would be needed. He's told me several times that it's his opinion that we don't need that actual wording to include it in VFC. It's a little hard to say in this situation where we might be saying in Colorado "nobody should get it under VFC" versus some other places. So I'm not quite sure how we would balance it, but there—in his opinion, there are ways in which we can include something less than a clear "is recommended."

PETER: The other point about making a category for recommended, I mean, I can think of circumstances where clearly physicians should be told to give this vaccine. For example, if it's recommended for children and you've got a person going to Boy Scout camp in—what's the name of that place in Rhode Island where they all go, Barbara; I can't remember—but you know, a person that goes down there or goes to. . .

SCHAFFNER: Gordon's Pond.

PETER: What?

SCHAFFNER: Gordon's Pond.

SCHAFFNER: But one of those places, I mean, we should say more than "should be considered, but should be given." I mean, these are people that are living in cabins where they're tick-infested and the risk of disease is significant. Now that's, you know, once the vaccine is approved for the age group.

MODLIN: Alright. Rich, you had a comment?

CLOVER: Yeah. Just to follow-up on what was just said. I'm a little bit uneasy with a "is recommended statement" at the current time without safety data in populations which we have not tested, and especially without safety data as it may relate to booster doses. I think it's intriguing there's a correlation between the presence of anti-OspA and the development of cross-reacting antibodies. I've got some concern about what booster doses may do that may enhance that. Until that safety data is out there, I am uncomfortable with a strong recommended statement.

SNIDER: It seems to me the problem is—again, as Rick was pointing out and as I've tried to elicit—we've got a two-stage process. What's up on the overhead is just the first cut—is the geographic cut. What we don't have

is the language for the individual risk assessment that occurs on the second cut.

MODLIN: Jose?

CORDERO: I think the whole issue about covering with VFC is going to put us on the road that a lot of caution signs are going to be raised that will need to eventually be addressed; for example, the example of the Scout camp. Someone from an area that is worried there is no Lyme disease goes to for the summer, is that child then eligible for receiving the vaccine in Colorado before they come? Like if they're traveling there, what happens if someone—let's say that we have it only up to age fifteen and seventy. What about if this vaccine is given to someone below this coverage? There is going to be a set of major issues. . .

MODLIN: Sure.

CORDERO: . . .on the cost and coverage that, I think, that the working group is going to have to think very critical.

MODLIN: Right. I would suggest that we consider putting off thinking about the VFC issue because clearly, we don't—that's only going to be an issue once we have some pediatric data and that's a ways off. Obviously, we need to be thinking about that. I think what Dave and his group now needs is some guidance and some direction with respect to preparing the next drafts of the statement.

SNIDER: But I think the implication of what Jose said is, again, this one-step, two-step and what the very low to zero is—"not indicated unless." At the second step, you have to start addressing some of the issues, talking about it.

MODLIN: Right. I think Georges' comments are very appropriate with respect to whatever we say about children in this statement, and that is be very specific about the reasons why the Committee and others are concerned that the vaccine is not appropriate for pediatric use at this time.

FAGGETT: Dr. Modlin?

MODLIN: Yes.

FAGGETT: I want a point of information—Walt Faggett.
MODLIN: I'm sorry, Dr. Faggett.

FAGGETT: I'd just like a point of information for Neal Halsey. I wanted to know are there inner city kids involved in this study? We need to know if those

are inner city kids who go to camp who are under-immunized to start with. Do we have data like that, Neal, to help us in determining risk? Again, this speaks to Fernando's point about being inclusive of all populations.

MODLIN: Absolutely. Your point is well taken.

FAGGETT: Neal?

SNIDER: Are they included?

MODLIN: I'm sorry.

HALSEY: Are they included in terms of being at risk or are they included. . .

SNIDER: In the trials.

MODLIN: In the trials—in the vaccine trials.

SNIDER: Walter was asking about that.

HALSEY: No, the trials are usually being conducted in people who are living in high incidence areas. I can't—Dennis Parenti knows all of these. You really want people who are going to be staying there. Most of us have selected the high incidence populations who reside there and not so much those who move in. I don't—I can't give you an ethnic breakdown on the populations or where they're residing, but Dennis could a, you know, better job of that.

FAGGETT: I would just like to submit that the NMA Pediatric Section would be available to assist in this area. . .

MODLIN: Terrific.

FAGGETT: . . .put a pen on it now.

MODLIN: I appreciate that very much. Jane, and then we'll move on.

SIEGEL: Are there any serologic studies in endemic areas in different socioeconomic groups to tell us what the exposure is?

FLEMING: No. The question had to do with whether there was serologic studies that would inform us on the extent to which socioeconomic status influences risk.

CORDERO: One more comment. I guess that the more I hear in the discussion, whether it's coming from cost or in terms of the finding, is that they

really need to go on something beyond just the geographics because people are mobile. We have people that are moving; like a third of the population move in the course of three years. What do we do when people actually are faced with a child that may be going to camp and it's in a geographic area with low incidence but it's moving? I think those—I think that that's the kind of issue that we need to deter the "not indicated," but in this case, it is. I think that that's going to be critical in the practical terms of the vaccine.

MODLIN: Dave has some other things that he wants to accomplish before we wind up here, so let's continue on.

FLEMING: First, I wanted to thank you for the excellent and precise input that you've provided on this. I think what I'm hearing is that in general, people are okay with the proposed framework. What we need to do is explicitly consider whether or not there's a combination of geographic risk and occupational or other kinds of personal risk that would warrant a new subcategory of "is recommended." We will strongly take that under consideration and will proceed forward with the framework I've proposed. We're running late. There's been a number of comments about children. While we are not going to discuss that issue explicitly, I did want to give the manufacturers an opportunity just to tell you about where we are with respect to developing the kind of data that we think we all would need ultimately for kids.

PARENTI: Thank you. Let me start by saying that we had conducted a pilot trial in Europe in children ages five to fifteen—a study of approximately 250 children, half of whom received 15 micrograms, half of whom received 30 micrograms. They received three doses on a somewhat different schedule. They received it on a 0, 1, 2 schedule. The preliminary data or the data from that study suggested that there were no study events or safety issues, but also suggested that it was very immunogenetic in children. So with that, we've moved forward to a study which has recently started to assess the safety in a large cohort of U.S. children.

The study that we're currently conducting is a multi-center randomized double-blind placebo control trial, which is scheduled to have 4,000 subjects enrolled. They'll receive vaccine on a 0, 1, 12 schedule. It's a 3 to 1 randomization. We have an immunogenicity subset to evaluate obviously serum levels. This is—all the sites are in the U.S.; they're all in endemic areas. As Neal had pointed out, that's basically the only way to get subjects who are interested, you know, who feel that they're at risk. We plan to cross over the placebo recipients after unblinding and planned 36 months—at least 36 months follow-up in these vaccinees. We started enrollment approximately five or six weeks ago. We have approximately 3,500 children enrolled, so we'll probably just

need a couple more weeks for enrollment. Again, as somebody had pointed out, the data won't be available until at least next year.

MODLIN: Thanks, Dr. Parenti. In the interest of time, Fred, did you have any comments? Fair enough. Again, I think Dave, you've already summarized fairly nicely. I think that the Committee has not spoken obviously, but has given very reasonable feedback and certainly provided a sense of direction for the working group. I think it sounds to me like there's very strong support for the direction that you're going. We will plan on putting this vaccine on the October schedule in a prominent place and give it adequate time to discuss the details of the next draft. Let's break for lunch. We'll be back at 1:15 sharp to take up influenza.

GUERRA: The flu group, again, will meet in 1111A.

MODLIN: Let's call the meeting to order if we could.

SNIDER: Great, there's the bell.

MODLIN: Dixie, we don't quite have a quorum here, but I think we can get—but can we get started? Yeah; let's do. We don't yet have an official quorum, but nonetheless, I'm going to take the Chair's prerogative and go ahead and suggest that we get started. For Committee members who are here, let me urge you to review the drafts of the rotavirus document, the combination vaccines document and the Lyme vaccine statement, and try to get your comments on these statements back to the chairs of the working groups by—pardon?

HELMS: And the rabies document.

MODLIN: And the rabies document as well—thank you, Chuck—within a month, within four weeks of the end of the meeting so that work can proceed. This afternoon's agenda will begin with an update from the Influenza Working Group. I understand that Dr. Keiji Fukuda will be introducing the topic. We have a guest, Dr. Bob Belshe from St. Louis, who will be participating. Keiji?

FUKUDA: Hello. Is this working? Okay. We're going to spend about the next half an hour to 45 minutes going over some—updating you on some events related to influenza. I'll talk for about ten minutes and then I'll turn the floor over to Dr. Belshe. The thing that I wanted to do is update the Committee on some of the deliberations and some of the progress that's been going on within the Influenza Working Group and some of the things that we're trying to address. The primary issue that the committee or the group is trying to address is whether ACIP should broaden its recommendations for influenza vaccine to healthy children

and healthy adults. There are a couple of main factors which are driving this debate right now.

The first one is that Aviron will be imminently applying to market its live attenuated cold adapted influenza vaccine. This is a product that Dr. Belshe will be talking about in a few minutes. This is one of the main things driving this whole issue right now. The second thing though is that the potential for reducing morbidity and mortality by extending vaccine recommendations has been discussed for a number of years. The third thing is that, particularly vis-a-vis healthy adults, there has been a lot of discussion about whether this would be economically beneficial. I think it's probably obvious, but the potential impact of expanding influenza guidelines would be enormous. This would represent both a major shift in national vaccine policy to extend influenza vaccine to healthy people as opposed to people who are at risk for complications. Potentially when you think about it, this is addressing whether the possibility of vaccinating the entire U.S. population on an annual basis, and so the stakes for the discussion are quite high.

Now there are several primary questions associated with this kind of issue. The first one has to do, you know, what would be the individual and social benefits of this kind of move? The second issue would be the cost potentially would be enormous and who would be paying for this kind of effort? Thirdly, there are a whole number—a whole host of logistic issues which come up. Who would administer the vaccine? Recommending one versus two doses would have potentially enormous impact on the logistics of providing this vaccine. Another issue is what would be the impact on other childhood scheduled vaccines? Another issue is whether there is sufficient manufacturing capacity in the country and whether that could be expanded. There are a number of issues related to the risk of this kind of vaccine effort. For example, what would be the effect on immunocompromised groups, particularly since the Aviron product would be a live attenuated vaccine. Are there going to be long-term immunologic effects of vaccinating children on an annual basis, potentially for the rest of their lives? Then another issue is whether—I think we all have a sense that there is the great potential for a backlash effect in recommending more and more vaccines every year.

The Influenza Working Group is chaired by Dr. Fernando Guerra. The first meeting was held on May 11th and 12th of this year. This was a public meeting that was announced in the *Federal Register*. The main focus of the meeting was on healthy children and then on the potential role of a live attenuated influenza vaccine. We cast our net pretty broadly in inviting people to this kind of meeting because we know that it's critical to get as much input as possible on these issues. So on the

federal side, several committees and organizations were represented. The state was represented by CSTE. We invited the American Academy of Pediatrics; a number of academic experts were in attendance. Then the industry was also in attendance—both in the form of a PHARMA representative, Dr. Fred Ruben, and then representatives from Aviron.

There are several discussion points. The first day focused on issues related to vaccinating children, not specifically related to live attenuated vaccine, but just the issues related to vaccinating children against influenza. One of the points which was clear early on is that everyone recognized that vaccine coverage of existing high-risk groups among children is really dismally low. These are, for example, children who have asthma or children who have other sorts of conditions predisposing them to complications. Now a lot of the discussion really was really divided between children who are young—less than five— and then children who are older. I think in the children who are under five, there was really one main question and that is whether this group comprises an unrecognized high-risk group? Certainly there are data out there which suggest that rates of hospitalizations and mortality may be higher in the—or are higher in the very young compared with other age groups.

However, it was felt that if this argument were to be made, then really more data would be wanted to make this an absolutely compelling case that this is a high-risk group similar to other high-risk groups that ACIP currently directs its recommendations toward. It also brings up some very difficult questions. For example, if ACIP were to say that young kids were a high-risk group, it brings up the question of whether all contacts of young children should be vaccinated similar to current recommendations. This would mean all siblings, all parents, all other people having contact with kids—potentially an enormously large group. The discussion on children between five and eighteen years was really quite different. I think that it's recognized in this group that this is a group which frequently is ill from influenza and they—and school age children usually have the highest attack rates.

However, rates of severe illness are usually low in this group and rates of mortality are low in this group. So the major potential argument for vaccinating this group would be that by covering this group, you theoretically could slow the spread of influenza among communities and then potentially to other high risk groups. However, at this point, this remains much more of a theoretical possibility. There are studies going on right now which will be looking at this directly; notably, Dr. Glezen has a very large study in Texas which will be looking at this, but those data are not available right now. As always, a lot of the discussion focused on the economic considerations. The group was given a talk

by Martin Meltzer from NCID. I think Martin has really been very pivotal in doing a number of economic analyses on influenza. I think that we'll be hearing a lot about his work over the next couple of years. I think that a lot of Martin's work makes some very important basic points clear.

The first one is that in looking at economic cost benefit analyses having to do with influenza, there are a number of important factors, such as the attack rates of influenza for that year; vaccine effectiveness calculations for that year; vaccine costs and so on. When you look at all of those factors, the one factor which really drives the cost benefit analyses is mortality rate. This comes out as the single most important factor. I think that the other, perhaps most important point is that for influenza, as opposed to many other infectious diseases, the importance of these factors or the value of these factors varies on a year-to-year basis. The prevalence of infections can change; the attack rates can be highly different; hospitalization rates and so on can vary. So I think that the one thing that you should draw away from here is that it's pretty clear that any analysis based on a single year's worth of data for influenza can be misleading, and that to have a good—for the Committee to have a good grasp on the potential economic impact of this kind of move, you really want to have data from several years.

Now on the second day, we shifted the discussion towards the live attenuated influenza vaccine. That should be not "IV" at the top, but "LAIVS." I want to point out that live attenuated vaccines, there are several strong points about these vaccines. There is a great deal of research experience on these vaccines and many people in the research community feel quite comfortable with them. For most age groups, at least, the effectiveness is comparable to inactivated vaccines and potentially better in some age groups. Again, there's the potential for broader and longer lasting protection in some age groups. Another major logistical strong point is that you don't need needles to administer this vaccine. So far, there have been no unexpected major side effects coming out from the trials looking at these vaccines. However, you know, questions such as GBS related to live attenuated vaccines inevitably come up and that's an unknown risk right now.

However, there are also several concerns related to the use of these vaccines, especially in large groups. The first one is what would be the safety risk for some high-risk groups? Again, immunocompromised people come up as a major issue. A second issue has to do with whether these vaccines can cause interference with other vaccines, particularly other live attenuated vaccines given to children. Another issue has to do with whether one or two doses would be recommended. Again, this would greatly affect the logistics of giving these vaccines. A third—another issue which came up, which I hadn't really thought about,

was whether the introduction of influenza—of this new influenza vaccine—will begin to compete with some other vaccine efforts. Rotavirus vaccine was brought up as an issue; whether, again, bringing on many different vaccines at the same time or relatively the same time would cause some competition. Then finally, there are a number of issues about what the manufacturing capacity would be for this vaccine and what the egg supply would be if the market expands.

So the bottom line after a couple of days of intense discussions was that the idea of expanding influenza guidelines or recommendations really brings up a very complicated mix of both philosophical and practical issues; whether it ought to be done and if it is—if it ought to be done at some level, how can you actually implement something like this? I think that it's becoming quite clear that, you know, if and when these ACIP guidelines begin to change, they really need to evolve. They need to evolve in step with the evolution of a couple of other things. The first one is that as more data become available, I think it'll help clarify some of the issues which are unclear now. The second thing is that it's pretty clear that the guidelines really should not and cannot out-strip the manufacturing capacity in the country. I think that would cause a tremendous amount of confusion and anxiety.

So there are some fairly immediate action steps for us to take as a committee. The first one is that we—this is the first time we've announced it—but we will be holding the second meeting. The tentative, almost etched in stone date will be September 1 and 2 for another meeting at CDC. Again, this will be a public meeting and the focus of this meeting will be on healthy adults under the age of 65. I think it's very clear that we need to continue to coordinate the working group's efforts with the medical organizations and other public health organizations out there. I think for the Influenza Branch, we have several tasks to be working on. I think the first one is that to work on the prioritization of both the issues and the questions that need to be addressed. We can't address all the issues at the same time and we need to clarify what are the more important ones to go after first.

The second one is that there already is a huge amount of information out on these vaccines, but there's so much information, that's it relatively inaccessible and very confusing to people, so to try to clarify that a little bit. Then we need to begin actually drafting the new, the architecture of the new document. Then finally, we have in the meeting identified some studies which can be done immediately and which ought to be done. So we need to identify some funding for some of those studies. That's one of the things that we're trying to do right now. So anyway, I think I'll stop there unless there are any questions and turn the meeting over to Dr. Belshe.

SNIDER: I just have one question, Keiji. Vaccines administered intranasally as oral vaccines have the potential, of course down the road, to be administered by the individual patient instead of the health care provider, or certainly by someone other than a physician or at a place other than a physician's office, which would have advantages and disadvantages depending upon a lot of factors, including the safety profile and so forth. Was there any discussion about this in the group?

FUKUDA: Yes. There was discussion. In fact, I think that the company is envisioning that eventually, this vaccine would be administered in non-medical environments, you know. This could be pharmacies; this could be at home by parents and so on. I think that would—it's clear that that could potentially relieve some of the congestion in physician offices and so on, but it does bring up a host of questions. I think that John, Dr. John Abramson representing AAP, had spoken with a number of pediatricians about this. I think that his sense is that there would a great deal of reluctance on the part of pediatricians or clinicians to see those vaccines being administered outside of the medical setting, in part, because it would be difficult to keep track of what's being given and those sorts of issues. It also brings up a number of practical issues. For example, if syringe—if the child sneezes, whether they need to get a second dose or not, or whether something is dropped and it's not a—no longer a "sterile" syringe, whether it's safe. So I think there are lots of smaller questions like that, but it is an issue which was discussed.

MODLIN: Bill?

SCHAFFNER: Just to follow-up on Dixie, the National Vaccine Advisory Committee is also considering this question at the same time as you probably know.

FUKUDA: Okay. Well, let me turn it over to Bob. Bob, I think most of you probably know, has been working on these vaccines for several years. He just had an article come out in the *New England Journal* a few months ago on this vaccine.

BELSHE: I appreciate the opportunity to speak before the ACIP on our efficacy field trial with the cold adapted influenza vaccine. Let me comment that—let me take responsibility for the thrust to get the vaccine into the frozen food section of the grocery store because this is me that's going around saying that, not the company. The company has no desire to upset pediatricians and other groups involved and that kind of thing, but I'm not constrained by that since my funding comes from NIH. I understand that you've had a presentation previously from the company prior to the results of the efficacy field trial being released. So I'm going to go very quickly over some background information and then turn and talk about the field trial, its results, and then try and answer some of

the—a couple of the questions that were asked of us in the working group and that we hadn't yet done the analysis.

Well, the live attenuated vaccine is cold adapted. That means it replicates at 25 degrees in the laboratory, which is not a property of wild type influenza. It's temperature sensitive, meaning it will not replicate at 39 degrees, which is a property of wild type virus. They're attenuated in animals and the viruses have multiple genetic changes in several genes that are associated with attenuation. The characteristics then, when evaluated in seronegative children, are shown here. The infectious dose, 50; for a seronegative child was approximately 10^4 pfu. About 10^3 pfu per milliliter of nasal wash sample is shed in secretions. Reversion to wild type does not occur and we understand the genetic basis for that. It's because of the multiple genetic changes and multiple genes. Monovalent, bivalent and trivalent vaccines are well tolerated up to a dose of 10^7 pfu of each strain in the vaccine.

There is some interference between strains in some studies. Several strategies have been used to overcome that interference, including upping the dose. The most practical one to me seems to be to give two doses, and so that's what we did in the field trial. There are other things that could be examined, such as giving one strain in one nostril, another strain in another nostril or tinkering with the relative quantities of virus—more H1N1, relatively less H3N2. None of those things have been investigated as being very practical at this time. The vaccines induce both serum antibody and secretory antibody. So with that as background information, the NIAID and Aviron undertook an efficacy field trial. Year 1 data, I will present today. The goal of that study was to evaluate safety immunogenicity and efficacy in young children. This was the pivotal Phase III efficacy trial on which the pending PLA rests, as well as previous studies, of course.

We took the opportunity to evaluate both one-dose and two-dose efficacy. Year 2 is ongoing. This was to evaluate annual revaccination in the same study and one dose was given. We will have that data some time in the second half of this year. A study outline is shown here. The vaccine consisted of $10^{6.7}$ $TCID_{50}$ of each strain per dose. It included A/Texas, A/Wuhan and B/Harbin. Those antigenically matched the inactivated vaccine for this particular year. The placebo consisted of egg allantoic fluid, which was identical in appearance and smell to the vaccine. The vaccine is given by nasal spray using a very, very simple device that's very convenient. In fact, when we're doing adult studies, we do have the adults give this to themselves it's so simple. The randomization was 2 to 1; twice as many children got vaccine as placebo. They were healthy children enrolled 15 months to 71 months. Now eight of the—there were ten participating clinical sites.

Eight of the sites gave primarily two doses of vaccine separated by sixty days as the target interval.

Two of the sites—because of logistic reasons, primarily getting IRB approval—gave only one dose of vaccine. So we took that opportunity to examine efficacy of one dose as well as two doses. Safety data were collected using a diary card system. We performed active surveillance throughout the influenza season by telephone the family once a week and reminding them to report any illnesses that were thought to be influenza. We asked them to report very, very trivial things. Cough and rhinorrhea was sufficient to be reported and triggered a viral culture. So we then cultured all these illnesses for influenza. A case definition then was positive culture for influenza that was wild type virus and not vaccine virus. Any isolate occurring within 28 days of immunization was phenotyped to determine whether it was wild type or shedding of vaccine virus.

Two hundred eighty-eight children were randomized in the one-dose cohort, and 1,314 were randomized to the two-dose cohort. Now among the two-dose group, more than 97 percent actually received both doses of vaccine. There were only two children who did not get dose two because of a concern of a possible adverse reaction to dose one. It turns out both of those children had received placebo. So the overall study then consisted of 1,602 randomized 2 to 1 vaccine to placebo. The demographics of the participants is summarized here. The mean age is 43 and 42 months. Approximately two-thirds of participants were in day care or preschool. The mean number of children in the household was 2.6. Slightly more than half of the participants came from a household that had more than one child participating in the study. Children were randomized as individuals, but not as households.

We collected safety information with diary cards. Rhinorrhea was, of course, very, very common in both vaccine and placebo groups. It was statistically significantly more common in the vaccine group, particularly on day two and day 3. I'm showing you safety data from day two on this slide. So there's a slight increase in rhinorrhea— relative risk about 1.5; 1.6 percent of placebo recipients had an elevated temperature on day two; 6.5 percent of vaccinated children had slight elevation of temperature on day two and only on day two. The mean temperature elevation was 107 among the children with fever and the mean duration was 1.4 days. This difference was present only after dose one and only on day two. It was not present after dose two. There were no serious adverse events associated with vaccination. The first approximate twenty children from each site participated in an immunogenicity sub-study where we drew blood before each dose of vaccine and then after

the second dose. The results of the immunogenicity of that cohort are shown here for approximately 200 children.

The proportion seronegative to the various strains in the vaccine is shown in the left-hand column. So about half of the children were seronegative to H3N2 at entry, and two-thirds of the children were seronegative to influenza B and influenza H1N1 at entry. After dose one, 92 percent of the children seroconverted to H3N2 and 88 percent seroconverted to influenza B after dose one. It has been shown in some previous studies, but we did not—it took two doses for the majority of children to develop antibody to H1N1. Now beginning in late November, early December, there was an outbreak of H3N2 in all ten participating cities in this study. This figure looks at isolates from the community as shown here in this blue-green color. The scale is on the left-hand side for community isolates in the ten centers for H3N2. The white line represents isolates from study subjects and you read that number on the right-hand scale. You can see there's an outbreak in study subjects at the same time there's an outbreak of H3N2 in the community.

Then later on in February and March of 1997, we had an outbreak of influenza B in the community shown in pink and in the study subjects shown in yellow. Now when we analyzed the occurrence of isolates from our study subjects, we found there were fourteen isolates of influenza A or influenza B among the 1,070 vaccinated children. There were 101 isolates of influenza among 95 children in the 532 placebo subjects. Two of the placebo recipients had first an influenza A H3N2 isolate with the illness, and then later on had a second illness with influenza B. That's how we got 101 cases among 95 children. So clearly, it was highly efficacious at preventing influenza—both influenza A and influenza B. We do the standard efficacy calculation overall when the vaccine was 93 percent efficacious against any influenza. The confidence intervals were fairly tight on that between 87 and 96 percent with a 95 percent confidence interval.

In fact, every other measure of efficacy falls within this confidence interval, whether we're talking about one dose or two doses of vaccine efficacy against H3N2 or efficacy against influenza B. Now we're just now beginning to look at some effectiveness measures. On the bottom part—bottom panel is the figure I've already shown you on the occurrence of isolates in the community and in the study subjects. The top panel represents the relative of having a febrile disease in any given week for vaccinated children relative to the placebo group. The dashed line is the relative risk of one; anything below one represents a reduction in febrile illness. At the peak of the H3N2 outbreak in the community, there's a reduction in febrile illness—a relative risk of febrile illness in the vaccine group to .5 and that's statistically significant in that week.

Now we had the opportunity to culture over 3,000 of these illnesses. So this data I'm showing you looks at the analysis of these illnesses regardless of the result for influenza culture. So in the vaccine group, there were 1.8 illnesses per study subject, and in the placebo group, 1.9; that's not statistically significant. If we look at febrile illness, however, there is a significant difference. Vaccinated children had .7 febrile illnesses per subject and the placebo recipients, .9; that's a 21 percent reduction in febrile illness and that's highly significant. There's a high concordance between having a febrile illness and getting antibiotics. That resulted in a 28 percent reduction in antibiotic prescriptions in vaccinated children versus placebo recipients. Otitis media was commonly diagnosed: .4 cases in vaccinated children; .46 in placebo subjects. That's not significantly different, but febrile otitis media was significantly different: .14 cases versus .20 cases; it's highly significant—30 percent reduction in the number and the rate of having febrile otitis media. Most children got antibiotics. It was a 35 percent reduction in antibiotic use in vaccinated children versus placebo children.

Now here's some new data. I was asked at the working group, "Well, what if you just analyze antibiotic use overall?" So that's what this slide addresses. This is a brand new slide; I didn't even proof it. So I just see that this is "live attenuated," not "time attenuated," although thirty years of studies might say it's time attenuated. Live attenuated influenza vaccine—okay; this is the number of study subjects. Number of illnesses, 2,359; illnesses per subject, .20; among the placebo groups, number of illnesses per subjects, 2.3. This is all subjects, all illnesses. There's no significant differences. If we look at illnesses associated with antibiotic taking by the study subject, there were 905 in the vaccine group and 521 in the placebo group. That's significantly different. The antibiotics per study subject was .85; antibiotics per placebo subject, .98. That's a 13 percent reduction in antibiotic usage overall and that's significant.

Number of visits to a health care professional—so this would include emergency room visits or going to a primary care physician—1,321 in the 1,070 vaccinated children; 758 in the placebo recipients. That's a visit per subject rate of 1.23 versus 1.42 in the placebo group, 13 percent reduction; that's highly significant. So significantly less visits to a health care professional. If we look at visits to a health care professional with antibiotics prescribed, now that's different than this. This includes kids who got antibiotics from their mother, or their friends or whatever. So there's a difference here, and again, it's significantly different; same percentage, 13 percent reduction and that's statistically significant. So by any of these measures, we saw a reduction in antibiotic use. Now children who had no pre-existing antibody to

influenza respond with antibody when you give them H3N2 vaccine. Children, for example, with less than 1 to 4 pre-existing HAI antibody, 92 percent responded after dose one with antibody to H3N2. Children who are seropositive relatively infrequently get further four-fold rise in antibody; in this case, only 18 percent.

Now this is highly age dependent. Young children tend to be seronegative. In this case, if they were less than 24 months of age, 73 percent were seronegative and the older they get, there's a trend to more and more pre-existing antibody. So we asked the question, "Was the vaccine then more efficacious in young children compared to the older children?" We were surprised that when we broke down efficacy into these five age groups, there's no significant difference in vaccine efficacy as children get older, which suggested to us that it's something other than serum antibody that's correlating with protection. I'm grateful to Bill Gruber for this particular slide. He studied his subjects at their Vanderbilt Center for induction of mucosal IgA antibody responses in his study population participating in this efficacy trial. More than 80 percent of study subjects developed IgA antibody to each of the three strains in the vaccine after two doses of intranasal vaccine.

So then to summarize what do we know about the vaccine, more than 10,000 adults and more than 4,000 children have received one or more doses of a cold adapted influenza vaccine. The nasal spray is very easy to use and parents and children readily accepted the vaccine. The vaccine was safe and well tolerated. Rhinorrhea or nasal congestion was common on day two. The relative risk was 1.5 and low grade fever occurred infrequently on day two, a 6.5 incidence in vaccinated young children. Similar to other live attenuated viral vaccines, more than one dose was required to stimulate antibodies in the majority of participants. The vaccine was highly efficacious at preventing influenza A and influenza B. The occurrence of all febrile illness and febrile otitis media was significantly lower in vaccinated children, and in the new finding, antibiotic use was significantly reduced as well. So that the principal investigators of this study felt that the vaccine has the characteristics that make it desirable for general use to prevent influenza in children.

MODLIN: Bob, thanks very much. We are already running a little over time. You'll note that the session was largely for informational purposes only—largely for informational purposes, but I think we should take a little bit of time here for just a few questions and comments. I don't know, Fernando, do you as chair of the working group, do you have anything in addition that you want to raise at this time to help focus what we ought to be thinking about?

GUERRA: Well, I think that certainly he laid out the discussion very well. I think it's a very complex one. I think we need to look at, certainly, the cost

benefit studies a little more closely that are ongoing. I think that we need to look at some of the data related to some of the medical conditions, certainly, that seem to be important in terms of putting children into different risk categories. I think there is some sense that was presented to us in the May meeting that this seems to have a considerable benefit in protecting children also against recurrent otitis media in the younger population of children.

MODLIN: Alright. Other questions or comments? Chinh?

LE: I have a couple of questions on your study. I guess I'm referring also to the *New England Journal* article that's published for a little bit more data, detail. The enrollment was in August, meaning the vaccine was given in August?

BELSHE: We started enrolling in August. We actually enrolled in August through January.

LE: Oh, through January? Because I was thinking when you had the graph of the outbreak of influenza, especially the B, it doesn't seem to be as protective. I just wondered whether because. . .

BELSHE: Well, if you read the graph, the right-hand scale is isolates in study subjects.

LE: Yes. This one here?

BELSHE: Right, and the left-hand scale is isolates in the community. There were many fewer isolates. About half of the attack rate was for influenza B.

LE: So the reduction here, you know, this curvy line here?

BELSHE: Yeah.

LE: Is it statistically significant for B as well?

BELSHE: No. The only single week it's statistically significant is the one I pointed out at the peak of the H3N2 epidemic when analyzed by week. When we analyze the whole thing and lump it together, then you can achieve statistical significant.

LE: So I just wondered whether because the vaccine was given too far ahead before the B epidemic?

BELSHE: Well, the B is more than 90 percent efficacious at preventing infection with influenza B. That analysis is an effectiveness analysis looking at

reduction in febrile illness, which relates to the attack rate of influenza B in the community more than it does to the vaccine efficacy.

LE: The second question I have is the patients were healthy children without chronic illnesses. Did you discover any asthma-like reaction in children who may have reactive airway disease and whether this route would increase the rate of wheezing of those children with subclinical asthma?

BELSHE: There was no increase in asthma-like illnesses in vaccine or placebo recipients in the vaccine interval. With 1,600 children, there have been numerous events, many of which are wheezing events, but they don't appear to be related to vaccine.

LE: So is the vaccine going to be tested in children with asthma?

BELSHE: Yes. There actually has been one trial in children with asthma already. NIH and the company are planning a trial in children with asthma.

MODLIN: Chuck?

HELMS: Bob, how many sites again was the vaccine evaluated at?

BELSHE: There were ten.

HELMS: Ten different sites? Was the reduction in febrile illness and the reduction in febrile otitis consistent from site to site to site, or was this something that was seen just overall when you put your statistics together?

BELSHE: At any one site, the vaccine was efficacious at preventing influenza—culture-positive influenza. However, at any one site, if we just look at febrile otitis media, the numbers aren't large enough to achieve statistical significance in the effectiveness analysis.

HELMS: Was the trend the same?

BELSHE: The trend is the same in all ten sites, and you add those up and you get significance.

MODLIN: Barbara?

DEBUONO: On the otitis—febrile otitis media, how was that diagnosed—just based on clinical examination; were any cultures taken?

BELSHE: Yeah. We weren't the primary care doctors on this study. We simply recorded what happened to the children. So this reflects more of a real

world event, as you were. We recorded whatever the primary care doctor said that child has and so that's this analysis. Clearly, there is not standard diagnosis of otitis media across the country, and so this is a reflection of what's going on in the United States in pediatrics.

DEBUONO: I think it's interesting down the road if this should in some way get marketed as a preventive tool for otitis media as well, and whether or not there might any plans to kind of look at that further because I'm curious as to whether or not this otitis media is actually viral immediology or a co-existent bacterial infection that perhaps the patient was susceptible to more because of the influenza to start with.

BELSHE: Yeah. Several people have made that comment. Are we just preventing febrile illness, and therefore, we're preventing this basket of things that pediatricians are looking for some excuse to give antibiotics and calling it otitis. I think we really are preventing otitis media. The reason I say that, if I just look at the culture-positive cases, there were 21 cases of otitis media during an influenza episode that we cultured influenza. Twenty of those are in the placebo group and only one in the vaccine group. That's a 98 percent protection against culture-positive otitis media. So I believe that there probably is true protection against otitis media. Whether it's bacterial immediology or viral immediology, I don't know, but I'm not sure it matters.

MODLIN: I think every pediatrician on this panel will have their own bias and their own take on that issue. It's probably best not to open up that can of worms at the moment.

DEBUONO: Okay.

MODLIN: Are there other comments, questions? Bob, Keiji, thank you very, very much. We are running a little over. We certainly look forward to continuing progress of the working group. We'll plan on revisiting this. I'm not certain whether we'll do it at the October meeting or not. We'll have to see, but we'll certainly plan on doing it soon. Actually, probably with the working group getting together at the first of September, perhaps we should plan on putting it on the agenda if we possibly—if we have, if we can. Neal?

HALSEY: I wonder if we could just get a clarification from the manufacturer over what the plans are in terms of capacity to produce and what their intent with regard to the filing for use will be? I mean, there had been discussion in the press and elsewhere about giving it to all healthy children and so forth, or are you intending that the vaccine would be approved for high-risk groups? It does make some difference in terms of the planning and writing of the statements even though we're potentially a year away from really having it available.

MODLIN: Dr. White, can we have a short response to Neal's long question?

WHITE: Yes. Jo White, Aviron. The plan is we can make at least five million doses if we get approval. We don't know when we're going to get approval, but if it's in a year, five million doses. We plan to be able to double that, say, after each year for several years after that to upgrade that. The plan for submission for—it's eminent. We've said it's going to be in the middle of the year and that's pretty eminent. So you can tell that we're on the down side because they let Paul and I out of the office today, so we're pretty close to submission. We'll let Keiji and Nancy Cox know when we do that. The final question was "what indications?" We're asking for children, adults and concominant use with TIV in the elderly.

MODLIN: Thank you. We'll move on to the final item on the agenda, which is an update on the HIV vaccine trials that have just, as we all have learned from the media, have just recently gotten underway. I understand that Dr. Janssen will be introducing the topic.

JANSSEN: I'm happy to have the opportunity to introduce the next informational talk, which is a follow-up of a February 12th, 1997 presentation to the Committee by Pat Fast from the Division of AIDS at NIH when she talked about candidate vaccines potentially going into Phase III trials —candidate HIV vaccines. Bill Heyward also—who ordinarily would've been doing this introduction, or Kevin DeCock or anybody else in our division who's already left for Geneva for the International AIDS conference—wanted me to point out also that a year ago, President Clinton made it a goal of developing an effective HIV vaccine within the next ten years. I think what Don Francis will be talking about is the beginning of the next important phase toward trying to achieve that goal. What Don is going to be talking about is the initiation of the first Phase III HIV vaccine trials in the world. The candidate vaccine is a bivalent subtype B/B which will be tested, as we've all read in the media, in the United States among gay men and also trials will be begun later this year in Thailand. That will be a bivalent subtype B/E gp120 vaccine. In Thailand, it will be tested among injecting drug users. I'm pleased to introduce Don, who's putting the slides in the tray. Don Francis, who I think many of you may know from his twenty years at CDC working on hepatitis and HIV, is now the President of Vaxgen, Incorporated in south San Francisco, California. It's a spin-off company from Genentech for the development of HIV vaccines.

FRANCIS: Thank you very much. Good timing because I just had a discussion with the IRB here in terms of the Thailand trial. I have an airplane for Europe and Geneva in about 2½ hours, so we're going to fly through this as fast as we can. Let me thank you for inviting me. This is—I'm

sure Aviron feels the same feeling that I have. With everything going on at the same time, it's hard to settle down for a moment. Maybe in Geneva we can, but my experience in international AIDS conferences, not to mention I'm getting more cynical time. I'm not sure anybody but a small group of people, mostly in this room, really cares about vaccines because it's an extremely hard field outside of this room to discuss and have people understand. What I'd like to do is go through a lot of the data. How much time do I have?

MODLIN: Good question. We have about, yeah; we have about an hour.

SNIDER: For your plane?

JANSSEN: Well actually, it's both. I guess that's true. I really shouldn't ask you. I'll be flying out of here like everyone else will. I'll be going through the development of this whole thing, going through some of the milestones, dealing a lot with the monovalent vaccine, and then dealing with what we've seen with the bivalent vaccine, and the data that we used to generate the bivalent design—that is to break through infections and actually looking at it—and the plans for the next couple of years. Does this work? Look at that. This is a pointer I think. Good. Thank you. This is just a cartoon of the process here. Genentech started this about fourteen years ago now: working through with selecting the appropriate antigen, seeing if it'll protect chimpanzees, moving to humans, seeing if it was immunogenic in humans, then ultimately, seeing if it'll protect humans. We are at this stage now having recycled through this several times with successes and failures over the years.

The logic for selecting the appropriate antigen, despite much of what you hear, is that neutralizing antibodies do work and alum adjuvanted vaccines can protect against infections in general and HIV in specific, at least in chimpanzees. There were lots of early studies by Genentech and others showing that neutralizing antibody was directed, as you might expect, to the envelope glycoprotein. Then the question was, "Within that envelope glycoprotein, what strain are you going to use?" We looked at the principal neutralizing determinant. Although there are several neutralizing determinants of HIV, we just looked at the crown of the V3 loop and you see this whole diversion of different sequence. We are, strangely enough, typing this virus by sequence, which is probably the worst possible way you could type a virus. At least to begin with, we have that and I'll show you some movement where we're trying to join sequence with neutralizing epitopes. MN was clearly the most—the MN sequence of GPGRAF at the crown was the most representative virus around at that time. So after making an initial vaccine with 3B, recognizing that 3B was a very unusual isolate, we moved to MN, which was a much more typical one.

The process is identical to hepatitis B with the snipping out of the envelope sequence using CHO-derived cells to produce gp120, and then use that to induce antibodies to neutralize the virus. The wonderful thing about recombinant technology, as you all well know, is you get such nice, clean proteins where you can truly inject what you're planning to inject and not all the other material that you get from other vaccine preparatory methods. Now we've used the chimp extensively to guide our vaccine development. There's been all of these amazing discussions about the chimpanzee not being the ideal model because it rarely develops AIDS. We are not using it as a model for AIDS. We are using it as a model for directing us of whether we can prevent infection with the presumption that if you can prevent infection, you can prevent AIDS. So it's an extremely good model in that sense, although tough no doubt in terms of a standard.

Because of the rarity of chimps and the expense of the chimps, the challenge doses have been 100 percent infectious doses because in these studies, you have one or two controls. At 60 K each, you can't afford too many of them although the inoculum are well established in multiple animals by the time they are used. It is a very effective animal, not ideal no doubt, but no doubt an effective animal because all of them will get infected. It's probably the natural host of HIV. The challenge doses, at least with the 3V vaccine—unfortuately, 3V has infected two humans and clearly causes disease in humans. The SF2 challenge is a virus that came from a person who ultimately died of HIV. So they're presumably viruses that no one would want in them. Now these are the chimp studies. I am ignoring the first one, which was a failure which really knocked the whole field of HIV vaccine development back with Phil Berman injected the first animal with the 3V LAI vaccine challenged with this virus and the chimps were infected.

Tim Gregory and Phil went back to the drawing board, looked at the actual preparation and found out that there was proteolysis at the V-3 site and elsewhere, and that this was not indeed a decent vaccine; went back and developed a manufacturing procedure that would avoid that proteolysis and did the initial experiment that was published in 1990: the first protection of a chimpanzee with a vaccine from LAI and a challenge—homologous challenge—from LAI, which is the French LAI 3V isolate with doses that will produce 100 percent of infections in the control animals. I think this had two controls and this one had one, and that there was no variance obviously with a homologous challenge between the envelope of the vaccine and the envelope of the challenge. Two out of two animals were protected here.

The second one was a more arduous study using MN as the vaccine. Then there was a primary isolate of SF2 that had never been to continuous cell lines. It had just been in PBMCs. It was non-

neutralizable by the chimpanzee serum in the primary PBMC assay. Twenty chimpanzee dose—infectious dose 50s were given. Here, you've got an envelope variance about halfway down the world's variance of about 18 percent of the whole 36 or so percent of the world. These are both subtype B viruses, but quite a variance in terms of envelope sequences and three out of three were protected. This protection is documented by both no seroconversion to core proteins in the virus, no virus isolation, and they get a PCR. So this is true sterilized immunity. For those that say you cannot induce sterilizing immunity, clearly you can. Now the good news about this is you can induce protection. The bad news is we don't know how long the protection lasts. These animals were challenged about six weeks after their last boost. So they showed you could make a vaccine, but didn't give us a good correlate of what the protection was—whether there are certain levels of neutralizing antibodies were protective, et cetera, but you certainly could make a vaccine.

From that, we moved on to human studies. I just want to highlight here that we are ultimately—our hope is to make a vaccine for the world and that clearly, we are giving safety a high priority in our design. Now some people would say we're stupid because we are making a vaccine that balances safety over maybe efficacy, but at least for the first cut, we can see that we've got efficacy in chimps. Now we can make sure that we are maximizing safety. Purified glycoprotein— this stuff, as you saw from the gel, is what it's supposed to be. There's no live virus in the preparation at all ever. We just used recombinant technology to make it. We have no viral DNA detectable as has been required from these products by the FDA and other CHO-derived material having minimal DNA. We're using alum as the adjuvant. We've done some experiments with QS21. It's interesting, but at least at this point, not having the issue of having a new adjuvant there will be—will negate the concern about having a new adjuvant. We've had extensive toxicological, including development issues, since we've been in newborn babies with this vaccine already, not to mention pregnant mothers.

These are some of the toxicology with the 3V and the MN, including here neurologic development. Our concern was that with gp120, it was described as having some neurotoxicity. So both we and the FDA were concerned about development, especially since we were giving this to newborn babies and to pregnant mothers. So we did extensive rat neurotoxicity studies and developmental toxicity, both to babies and to pregnant mothers, and saw nothing. Then the safety profile in humans—we've given the vaccine now to over 1,200 or 1,300 individuals to date early on with extensive clinical monitoring, including hematological CD4 counts concerning whether the CD4 counts would drop only in the standard kidney and renal functions. As you see, we've

given it to uninfected individuals including newborn babies; infected individuals including pregnant women and infected women.

These were initially done. The large-scale study was to see if there was any effect on the HIV-infected individuals. That was published in *Lancet* and didn't show any effect as I think one might expect. It certainly didn't show any harm or accelerated disease, which was reassuring when it comes to vaccinating people. If they are infected, it doesn't seem gp120 will affect them at all. The only thing we've seen as far as an adverse reaction has been mild reactogenicity at the injection site. Here are the results from the Thailand study and the U.S. studies combined. Bob Belshe just left, but these are his results from the MN study, at least some of them. What you see is that pain and inflammation are the sole side effects we see. In the top line, both of these are placebo. You really don't see much difference in the vaccine versus the placebo. Indeed, you see a reverse situation in Thailand with a small number of individuals. More complaining of pain at the injection site received alum than who received alum in the vaccine.

There are some good, few centimeter-wide inflammatory reactions of individuals. We've actually asked the question whether inflammation was good or bad and still don't have enough data to show whether that—but there was a trend, actually, that having a red arm was a good thing in terms of ultimate antibody protection. This is Bob Belshe's slide actually from *JAMA* with the Phase I and II study. I have this on just to show two things: one, this was a trial of three different doses of 100, 300 and 600 micrograms, and then a 300/300 combined dose here, which is important because we're going to ultimately move at the end of this presentation to a bivalent vaccine. What we saw was a slight lag in the 100 microgram dose here. This is optical density that correlates very well with titre, actually, with doses given at 0, 1, 6 and 12 months. We see a good response slightly lag from the 100 microgram dose, but all the rest of them were parallel before except for 100, and then subsequent, all of them together. There's no difference in the 300/300 compared to 300 alone. We got a declining antibody with time with excellent anamnestic responses out to twelve months. I'll show you the neutralizing data and I'll show you the decline in the long one.

Here we show that the dosage, we just targeted at 300 micrograms subsequently as an adequate dose. It looks like 100 even, although it lags in the early months, would be also decent. This is just to show that the percent positive on the same slide. I'll show later that it's interesting that the maturation—this is the geometric mean titre of individuals; these were done at Duke—of the neutrals, but they run about—this is two weeks after each of these doses, and the neutral or geometric mean is somewhere between 1 to 150 to 200. You get your maximum boost way out, so it looks like that there's a maturation process after the six-

month lag and then a boost subsequently. I think on the next slide, you can actually see this. This is compressed a little bit because it goes all the way out to a year after the last dose: 0, 1, 6 and 12 month doses. You see here the geometric mean titre of these individuals is really twice of what it is in these. Then there's a decline over time. One person actually becomes negative by neutral about half a log here and about a full log drop in titre after a year.

We do not know at what level is good or bad in this case, but as I will show you, we're being very conservative on the Phase III. We're actually going to boost every six months in the Phase III to ensure that we keep the titres up. In addition to the antibodies that I showed you, I showed you gp120 antibodies with good antibodies to V-3 loop. As I'll get to in a bit, we're using V-2 as a good differentiator between the different strains since they overlap so much in their backbone. CD4 blocking antibodies are present in everyone and block at the binding site; the neutrals, I mentioned and both the laboratory strains that I showed you. We also—the highest titre individuals, all of these will neutralize, a variety of primary isolates in the PBMC culture. I'm not sure what that means, but we would like to have some assay system where we could look at serotyping of the virus. This is not a very sensitive one, but at least we have an assay system that gives us some feeling of the antibody titres to viruses that are out there in the field. It's good ADCC has been published by Belshe, et al., mucosal antibodies similarly.

We have not published the DTH. We have some interesting data that we went out to those individuals who are way out there on the right, and then took 10 micrograms of material and put it interdermally in. I think three-quarters to 80 percent of them got greater than 10 millimeters reaction to gp120 when given interdermally. Again, I'm not quite sure what it means, but at least there's long-term memory if nothing else, but we knew that from looking at the serologic response. This is just what we've called the SIV; a cartoon of the SIV work that you've seen in many other vaccines, but just thinking about HIV as multiple serotypes that we really do not understand at this point. We are using the ultimate empirical science when you've vaccinated people with MN: looking at what breaks through with MN and then try to add in a bivalent vaccine, and then with the future, looking what breaks through in the bivalent vaccine, and then recycle that into one vaccine at this point until we have a better serotyping system.

This is the first example of that that we had. We have nine break-through infections in our at-risk individuals who were vaccinated. They were vaccinated; some of these were obviously well before. They should have immunity—but we used all of them here, in this case, looking at seven—and compared those to the other break-through

infections in a parallel study with another vaccine, and then having control groups of existing cohorts that were selected at the same time in the United States. There were not all from the same geographic area, but looking at what would be expected in terms of the MN defined, at least the principal neutralizing determinant at the crown. What it should be is we've seen from large studies, as I showed you in that previous slide of about 600 combined studies in the Los Alamos database, that about 65 percent or so of circulating viruses should be MN in infected people in the United States, both incident —these are incident infections and in prevalent infections.

What was saw was actually the opposite in the MN immunized individuals—a small number no doubt, but interestingly in two different studies is statistically significant at .05 to .03 compared to what would be expected. However, this is not a placebo group. This is not a placebo group in the vaccine trial. So the data is not as hard as you'd like it. Also, it doesn't give you any understanding of whether the vaccine is efficacious. If indeed it were efficacious and it were SIV-ing out different strains, this would be a nice finding, and then it's different than what you expected. Now with that, then Phil Berman did an extensive job with these break-through viruses. These are the break-throughs—this is one, two, three, four, five, six, seven break-through viruses—and then did a whole variety, and this is published data now, a whole variety of studies looking at both the important neutralizing sites. B3, C4 and V-2 were monoclonal antibodies could document that if there was a change —if there was a sequence alteration, that the virus would be non-neutralizable by monoclonal antibody types, and then comparing the MN strain, which would be—all of these would be homologous if they were positive to MN, and asking the question was it—were the break-through viruses homologous or heterologous compared to the vaccine strain?

Except for this one individual here who, by the way, got vaccinated, broke through only a couple of months after his last vaccine, which was really very much MN-like in terms of sequence. Interestingly, Phil expressed all of these, and made gp120s with all of them and then in competitive assays. It's in the manuscript as published. It was really quite different in terms of its serologic or its immunologic binding reactivity. So he's a very interesting individual. The rest of them were all quite different in terms of the primary neutralizing sites on gp120 and were therefore different than MN. So with that in mind, Phil went into the laboratory and pulled out different strains of virus that we had from our therapeutic studies—let me go ahead and now go back—and took these V-2, V-3, C4 domains and selected ones that had the sequence variation that were complimentary to MN; that is that were now neutralizing monoclonals if they had this variation, as I showed you in

the plus and minus last time, and the flanking sequences for V-3 and selected a primary—another virus called GNE8.

Now what happened—this was purely a structural sequence section process—but what happened in the meantime was there was the discovery of the two different co-receptors for gp120 or HIV on various cell lines; that is that the macrophage atrophic viruses and the T cell atrophic viruses were differentiated. That's been one of our problems in terms of serotyping the virus because the only ones we've been able to get to grow in continuous cell lines and get good neutral assays developed have been these that have CXCR4 as the co-receptor versus the macrophage atrophic viruses that have the CKR5 as the co-receptor, which with CD4 allow for the viral entry into the cell. This discovery was made independently of the selection of this virus, which was selected really for its neutralizing sites. Interestingly, and I guess pretty obviously if you look—you can translate this to the V-3 flanking sequences—is that indeed this is a primary macrophage virus that has the CKR5 co-receptor. It's a non-syncytia inducing virus and indeed is a primary virus.

So that independently, we came through a discovery of different viruses. Are they serotypes? I do not know. As a matter of fact, we're not sure that this is essential for serotyping all of the primary neutralizing data. It's interesting when you mix the two together and there may be some advantage in terms of laboratory assays. In terms of pure empirical development and selection of a bivalent strain for the United States, we came up with not only complementary neutralizing sites, but also phenotypically different viruses that have different co-receptors. So this is the virus that we're using for the United States Bivalent Study: the MN, the continuous cell line, syncytia inducing virus. We've got all the work done on the Phase I/II studies and GNE8 in a bivalent 1 to 1 mixture of 300 micrograms each in alum.

Now interestingly, this is what—if you take these neutralizing sites of the four neutralizing sites, including the V-3 loop—and this is MN; this is GNE8 and this is the combination—if there is, if these indeed are important neutralizing sites, you see a very interesting addition. That in this slide, green is good; purple is better and yellow is bad— that is having the neutralizing sites present. MN is relatively mediocre alone as we've subsequently found. GNE8, on the other hand, by itself has lots of green and lots of blue; that is lots of four out of four of the neutralizing sites as determined in terms of prevalence in the United States, and then combining them together is a very crude picture of it, but was reassuring when we looked at all the sequences in the databases that are representation that was fairly good.

Now what we did was we went to the FDA Advisory Committee and to the technical committee in Bangkok, who are overseeing the advance into Phase III. We're asking the question of what we would do for determining if the bivalent vaccine was indeed immunogenic. We clearly did not want to invest in a Phase III trial unless both strains were immunogenic, and yet, putting them together is relatively difficult to decide if they are indeed immunogenic in the final product. So what we did was look at several different assays and ultimately came up with a peptide ELISA assay. The GNE8 will score very, very positive; that is even though it's not in the vaccine because the backbone is shared so much across the antigenic structure of this, that you will score very positive. So this could be a useless antigen in a bivalent vaccine. If you use gp120 as your score, you would not detect its effect because obviously, it didn't exist in this vaccine and yet it scores very positively.

The animal studies though showed that we could do, in both directions, an effective result if we used a peptide from V-2. Here is MN immunized individuals that scored very well. This is two weeks after the one-month dose; this was the second dose. Two weeks after the second dose, you can see that three-quarters of the individuals scored positive for V-2 to MN who were immunized with MN, and importantly, only 17 percent scored positive for GNE8. So as with our animals, the human data showed that the V-2 was a very good selective assay to determine immunogenicity. So what we did then was do a ninety-person in the United States just like Bob Belshe's study in the Phase I/II, but with a bivalent vaccine containing of each antigen 100, 300 and 600 micrograms, and with basically thirty people per group, and then did assays of gp120. As you can see, everyone tested positive after two weeks with gp120.

We then asked the question, "If we use V-2 from GNE8 and V-2 from MN, did you see an antigen-specific serologic response?" OD is here in terms of the relative titres. "Did you see a dose response?" The bottom line is we knew we'd get it with MN because we had a lot of—we knew that three-quarters to 100 percent of people would seroconvert right after two doses of MN. We did not know what it would be like for the second B isolate. As you see, everyone—very high response rate from the thirty individuals and that there was some dose response, but it was very—if we get this kind of response, we know that on the third dose at six months, 100 percent of people will seroconvert and it won't make any difference whether you use 100. We've gone ahead and chosen the 300 microgram dose for the Phase III just like we had seen with the Phase I/II. So it would be 300 micrograms of each antigen: GNE8 and MN in equivalent amounts given at 0, 1, 6 and then we'll boost onwards.

So to summarize where we are, we've gone through a long, over a decade process of selecting the proper antigen. I think we have representative strains now. I didn't mention that we've developed a production process, which I must admit, I was very naive about when I left CDC and went to Genentech. This is an incredibly arduous and challenging job to be able to produce something that's going to be the same each time. It's both safe and potent, and it's consistent. Genentech is still our partner in this and they're continuing to produce vaccine. We have—I think many of you know we've done this at market scale and have 300,000 doses of the MN antigen in the refrigerator. It is highly stable now to—what—six years and it's nice to have a process that should we have a vaccine, that we can make for the world. We can protect chimpanzees as I showed you. We've had very good animal and human data. We have a very good immunologic response in humans. The remaining question is will the humans react like the chimpanzees and indeed be protected?

I'll just mention here parenthetically that this is the Thailand vaccine, the bivalent B/E vaccine, which has all the similarities that I showed you with selection of the B/B vaccine, except that this is a Thailand/E virus. It is also a primary isolate and also has the same complementary epitopes, but here, it's got the prevalent GPGQ motif that we see in most of the world's HIV—the GPGRAF or the B is somewhat unusual. Most of the crowns are GPGQ. This is the virus that we're using for Thailand. I will not mention any more about it. I'll just throw this up. It's the old Phase III study of the hepatitis B vaccine that I did it seems like 100 years ago. Just to remind you of what we saw with hepatitis B, this is the placebo group on top, vaccinees on the bottom with core seroconversion in yellow, and viremia in red as with HBSAG. The end point here was the seroconversion to anti-HBS or HBSAG; that is to be—I'm sorry—anti-core. With a vaccine, it's anti-HBS. If an infection was documented as people who had core antibody and that were prevented from infection, or infection was prevented if they didn't have anti-core or if they had anti-core, whether they had continuous viremia.

What we saw very early on was a predominance—we had an ultimate elimination of infection, but we saw a predominance of anti-core seroconversion without viremia with hepatitis B. These are identical end points that we'll be using for the HIV trial, but just using different laboratory techniques to get them. The two studies, as I mentioned, you have B/B formulation in the United States, the B/E formulation in Thailand. It'll be primarily gay men in the United States, but heterosexual at-risk individuals will be admitted. They're IV drug users in Thailand, but the incidence in the United States is estimated to be about 1½ percent. So in order to have a lower bound of 30 percent, we'll need 5,000 individuals in the United States and 2,500 in Thailand. As I mentioned before, this is a three-year study, but we're going to be

giving boosters all the way out until 36 months. It'll take a year accrual, so there will be some people who will have about a year and a half follow-up to be able to see if there's break-throughs after. We've decided to be conservative and work out the schedule later, and maximize our chance of success in the studies at least at this stage.

The sample size is that we will assume no protection for the first three injections; that the annual lost to follow-up rate—I'm sorry; this is Thailand. It's 20 percent, 15 percent and 10 percent. In the United States, it's about half of that. There'll be a twelve-month recruitment period with no—we don't count any of the time in the first six months of the study. It's only after six months where there will be—where we're accruing the sample size. The sample size of the United States, as I mentioned, was based on 1½ percent incidence; in Thailand, 4 percent. The standard vaccine evaluation, vaccine efficacy computation will be made. That's it. I didn't put on here; I should've. I have in my briefcase lots of data in terms of the primary neutralization data that we have, primarily from the B/E vaccine, but also from the B/B. We have, interestingly, some quite broad cross-clayed neutralizing ability in the primary assay. The difference in the primary assay is that the titres you get are only 1 to 10, 1 to 30, 1 to 50, sometimes up to 1 to 100. It's a very insensitive assay because you're using blasted primary lymphocytes as your target cells. With that, I will stop.

MODLIN: Don, thanks very, very much. Before you dash off to your plane, we have time for perhaps just a couple of—do you have time for a couple of questions?

FRANCIS: Sure, happily.

MODLIN: Comments from anyone in the room? Many of us has heard you or others present much of this information in the past. Wow, you can tell that the. . .

FRANCIS: It's getting late.

MODLIN: It's late on the second day. Stan?

FRANCIS: Hi, Stan.

PLOTKIN: Don, I was interested by the DTH data. In view of some course by Walker, et cetera, what would you make of the—well, I take it would be CD4 responsible for getting it. How much influence do you think they have?

FRANCIS: Stan's question is that there has been clear correlation with survival associated with CD4. Actually, Jeannie Mackalrath is doing staining,

subtype staining on these biopsies from these individuals. I do not know the results of that yet; I don't know if she does. I don't know what they are, Stan. I think it's interesting, but I'm much more empirical at this point saying that there is an immune reaction going on. We can protect chimps and let's see what happens in humans, and then figure out what the important one. That is interesting that we have a clear DTH response that I think are probably CD4 helper cells presumably. We see that in lymphocyte transformation studies; we see that from just the pure anamnestic response you see serologically. So it's a new piece of data that I don't know what it means to be honest.

SNIDER: Don, what are the immunologic parameters you're going to look at routinely in this trial? I'm sure you're probably going to save stuff too.

FRANCIS: Well, we're saving everything on these folks in terms of serum. Then we will take a random sample of 5 to 10 percent of the individuals an run multiple assays against—both binding assays and functional assays, CD4 in neutrals. Then the infected individuals, we'd go back in their serum and look at their response, and see if—and that's in a case control fashion—if there's a difference in response in the people who broke through. In addition, all the viruses will be examined in infected, the placebo and the vaccine recipients. I hope we're in another assay system besides sequencing, but we're planning on sequencing and indeed expressing a lot of these. That's an awful hard way to do vaccine work, but that's at least our plan now. If there was a good serologic system in the future, maybe we can actually typing of these in something besides this primary neutral assay system.

SNIDER: What about cytokines?

FRANCIS: At this point, the cytokines and the genetic sequencing of some of the individuals, I think we're seeing that some of the sites—especially the NIH sites that we are supporting now, but the individuals in those who have academic abilities will be looking at some individual subsets of the vaccinees and the infected individuals. Those are yet to be worked out, but there's a lot of interest in it obviously. In the United States, we've just started now. We probably have a dozen sites or so on board. As you know, one site has already started, but it'll take a full year to get everyone in the study. We'll have probably—it'll be North America, I think, in total. We're talking to Canadian sites and to the Canadian FDA, and will probably move into sites there. To get 5,000 people, we'll need lots of sites.

MODLIN: Other questions? Don, thanks very much.

FRANCIS: Thank you.

MODLIN: Nice to have you back; have a good trip. I have heard nothing about anyone interested in making a public comment, so it's too late. Thanks to everyone for what has been, in my view, a very successful meeting. I wish those of you who are traveling to have a good trip back. The meeting is adjourned.

[*THE ACIP MEETING ADJOURNED ON JUNE 25, 1998 AT 2:50 P.M.*]