ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

February 11-12, 1998 Meeting

Verbatim Transcript

MODLIN: Good morning. If we could call the meeting to order, please. My name is John Modlin. I would like to welcome everybody to the February meeting of the ACIP. We'd like to begin with the usual introductions and the conflict of interest statements. Perhaps we could begin with you, Marie. I think we have a quorum here so we'll go ahead and start.

GRIFFIN: Marie Griffin, Department of Preventive Medicine at Vanderbilt and I currently serve as the Chair of Merck.

HEYWARD: Bill Heyward, CDC representative from the National Center for HIV, STDs and TB Prevention.

LIVENGOOD: John Livengood, Director of Epidemiology and Surveillance Division, National Immunization Program.

CORDERO: Jose Cordero, Acting Director, National Immunization Program.

FLEMING: I'm David Fleming, Oregon Health Division. I have no conflicts of interest.

GLODE: Mimi Glode from the University of Colorado. I've had some negotiations about a vaccine.

HELMS: I'm Charles Helms, Department of Internal Medicine at the University of Iowa Hospitals and Clinics. I have no conflict of interest.

CLOVER: I'm Rick Clover from the University of Louisville. I've had an education grant from Merck.

MODLIN: Fernando, please introduce yourself.

GUERRA: I'm Fernando Guerra.

MODLIN: I neglected to note my conflicts. Either myself, or my wife or my children own stock in Merck. Dixie?

SNIDER: I need to ask if Jessie Sherrod is on yet? In any event, I wanted to say that Jessie is going to join us by telephone. She has unfortunately been involved in an automobile accident and couldn't make it in person, but is

joining us by telephone hopefully. Again, good morning to everybody. We'd like to welcome all of you to this ACIP meeting, which promises to offer a lot of work for us as usual, but a lot of interesting and important topics for us to deal with. As always, we at CDC are very appreciative of the members, the liaisons and all the people who come to participate in these meetings, and to help us make some of the important decisions that we have to make.

I'm pleased to announce to everybody, although it's blatantly obvious that our new Chair is John Modlin. John has been a member of this Committee for the past two years. I also want to welcome two new members to the Committee: Dr. Richard Clover, who's Professor and Chairman of the Department of Family and Community Medicine at the University of Louisville School of Medicine, my alma mater; and Chuck Helms, who has introduced himself as Professor of the Division of Infectious Disease and General Medicine at the University of Iowa College of Medicine. I also want to thank two liaison members who have resigned from the ACIP since the last meeting: Dr. Georges Peter from the American Academy of Pediatrics Red Book Committee; and Dr. David Scheifele of the Canadian National Advisory Committee on Immunization. I'd like to welcome the ACIP new liaisons from the American Academy of Pediatric Red Book Committee, Dr. Larry Pickering, the Director of the Center for Pediatric Research, Children's Hospital of the King's Daughters; and for the Canadian National Advisory Committee on Immunization, Dr. Victor Marchessault; and from the Secretario de Prevencion y Control de Enfermedades in Mexico, Dr. José Santos-Preciado. Dr. Santos-Preciado was unable to attend our last meeting and I'm pleased that he's here with us today.

Dr. Gordon Douglas, who is the liaison for Pharma and was not able to attend today is being represented — Pharma is being represented today, I think, by Tom Vernon. At least, we have drafted him to do that and hope that we're okay with Pharma and all the manufacturers in doing that. Also Kathleen, don't leave. I want to introduce you to a new staff member. As you know, keeping all the ACIP business on track and on schedule was a tremendous job, and the work has increased significantly in recent years. Although Gloria has done a tremendous job, we began to recognize that she was beginning to be overwhelmed, and we're delighted that we were able to get Kathleen Johnson to assist Gloria. Hopefully, this will help everyone — certainly me — but everybody on the Committee. So Kathleen, we're glad to have you.

The members who had a yellow folder — I think several of you have yellow folders on your seat at your place — must sign the waiver letter and return it to Gloria before you can participate in this meeting, so if you would do that immediately. You will find in your notebook a yellow sheet with e-mail addresses. Please check your address for accuracy. If you

find an error, please let Gloria or Kathleen know your correct e-mail address. In the future, we hope to use e-mail more to transfer information in lieu of faxes. We'd like to add that members of the public who routinely receive agendas through the fax, if you wish to provide your e-mail address to us, we will forward the agenda to you through e-mail. Please complete the yellow form in the back of the room and provide the information, again, to Gloria or Kathleen. When you're putting down your e-mail address, I think everybody probably knows, but it does often make a difference whether it's upper case or lower case, so be sure to use the right case when putting down your e-mail address.

I also would like to ask all the members to provide an up-to-date CV to Gloria by March 15th. If your document is compatible with WordPerfect version 7.0, you can e-mail it to Gloria; her e-mail address is GAK1@CDC.gov. For those of you not familiar with the logistics of the Committee — the seating arrangements — the appointed Committee members and CDC employees who serve as facilitators are seated at this inner rectangular table; the ex officio members from other government agencies and the liaison members from agencies and associations from outside government are seated at the table at the perimeter. Because it's important for us to hear all the comments, we have asked everyone to speak up of course. We do have two microphones available for those in the audience who would like to get up and make a comment or ask a question. So I would appreciate anyone who would like to comment to use one of those microphones if you don't have one in front of you, and for those who do have a microphone in front of you, please bring it close enough to you that we can all hear you well.

It would be helpful to the transcriber if you would state your name at the beginning of your comments. I know this is not something we've routinely done, but for reasons I won't take the time to go into now, we are having to do full transcripts of the meeting instead of just minutes. As a consequence, the transcribers may attribute a comment to the wrong individual if you don't identify yourself. So I know this is new, but try to remember to do that. As usual, I also will point out that the restrooms are located to the left of the lobby area in Building 1. If you take a right out of the auditorium, and go through the glass doors and follow the hallway to the CDC museum. Actually, there are some restrooms there in the museum. Also, there are restrooms near the elevators in Building 1. There are restrooms — I think they're still operational — down the stairs below here. The CDC cafeteria — again, I think probably everyone knows where this is — but Building 16, which is directly behind me on the first floor is the cafeteria where you can get some coffee at the coffee break and something at lunch.

Be sure and wear your identification badge at all times. Our guards have been instructed to ask even employees that they see everyday to wear

their identification badges. So please keep that out and visible. There is a snack bar which is down the first hall over in Building 1 if you wish to get a snack at the break. Dinner this evening is at the new Violette Restaurant; dining is casual; dinner will be $30, which includes tax and gratuity; a cash bar is available. We should have some pieces of paper in our notebooks about that. Circle the entree of your choice on the pink menu that's in your notebook and return that with the cost of the dinner to Gloria or to Kathleen by noon today. If you would like to see a menu, please see Gloria. We'll leave from the lobby of the Emory Inn at 6:45 p.m. It looks like all the housekeeping to me; now it's your turn.

MODLIN: Fine, I have a few notes. Let me begin by adding my own welcome to Dr. Helms and Dr. Clover, the new members of the Committee, and also our liasions, Dr. Pickering, and Dr. Marchessault, and Dr. Santos-Preciado. Welcome. I have a few announcements to make. The final minutes of the last meeting, I understand, are almost complete. Actually, Jeff Davis should be able to review and sign the minutes within the next few weeks. The Health Care Workers' Recommendation was published in the MMWR in December, and you should have a copy of that recommendation. The next ACIP meeting for this year — the dates are June 24th and 25th, and the third meeting will be on October 21st and 22nd. I understand that this auditorium is scheduled to begin renovations on July 1st. That shouldn't affect the dates of the June meeting, but I've been asked to tell you to please check your mail and the *Federal Register* notice in case there may be changes to the location of the October meeting.

Dixie has already mentioned that members and the people in the audience have commented at times it's difficult to hear speakers, so again, yet another reminder, please speak directly into the microphone, and again, I ask each of you to identify yourselves prior to making your comments. The meeting is being transmitted, I guess, by Invision to the Parklawn Building in Washington, D.C. It may be necessary from time to time for me to repeat the comments for the people listening in from Washington. Dixie has already mentioned about dinner tonight. I would like to remind everyone that we have several working group meetings that are scheduled at various times during the meetings today and tomorrow. The rooms that are available for these working group meetings are apparently quite small, and so we ask that only members of the working group attend those meetings. Really, I guess the rooms are not large enough to accommodate those who are not members of the working group.

The Combination Vaccine Working Group will meet in Building 16, Room 1107-A. I understand, Bruce, that this will be a working meeting at lunch time today. The Rotavirus Working Group met yesterday, and there is a room available for the working group at the end of the day today if necessary. That room will be the same room the group met in yesterday,

Room 4226 in Building 16. The full Working Group on Influenza is in Building 16, Room 1111. I should also mention that we have recently taken the first steps to constitute a Working Group on Lyme Disease Vaccine that will be chaired by David Fleming. The other members of that working group have not yet been appointed, but the constitution of that working group is under active discussion. We're hopeful that that group can get up and started shortly after the end of this meeting. Thank you. Dr. DeBuono was slightly late in arriving. Do you want to introduce yourself and note any conflicts, Barbara?

DEBUONO: Sure, pardon me. I'm Barbara DeBuono, the Commissioner of Health for the State of New York and I don't have any conflicts.

MODLIN: Finally, regarding disclosure, ACIP members who do have a potential conflict of interest should make it known. I guess that's already taken part. Members, regardless of a conflict, may participate in discussions of all issues provided full disclosure has occurred. However, persons with a direct conflict of interest cannot vote on any issue related to the conflict, but note only members voting — in other words, voting members at the inner table need to disclose their conflicts. The ex officio and liaison members are not required to do so. Members with financial conflicts of interest must abstain from voting on VFC Resolutions as well. Since the conflict may also appear to be present, such a member is allowed to introduce or second a VFC Resolution. ACIP has adopted a policy that prohibits a member with a financial conflict of interest from either introducing or seconding a VFC Resolution.

Okay. With that, the announcements are over with. We'll get started with the agenda today. Let me make it very clear that I fully intend to keep the agenda to schedule, and that I will apologize in advance to anyone that I get a little short with if you begin to go over. The Chair has a responsibility for, of course, seeing that we have a full and complete discussion of all the issues, but I also consider that I have a responsibility to make certain that we finish up on time because it's only fair to those who have planes to catch and want to get home to families, even here in Atlanta to do so. So I have every intention of keeping this on schedule if at all possible. We're actually a few minutes ahead, so let's go ahead and get started. John, is it you or Jose that will begin with the NIP announcements today?

CORDERO: Buenos dias. Can you hear me? I'll be brief and in the interest of time, I will only make my remarks in English. I'd just like to point out two things: one is about the session core functions process that we're involved in, and then I'll briefly mention a couple of personnel actions or activities. Some of you may know our budget for grant programs has actually been reduced for like 20 percent for this year. One of the questions that has come up is how much does it cost to actually run a state and local

immunization program? In trying to answer that question, we have begun a process that started with a meeting on January 26th where we tried to identify, with the help of a number of partners from the group sitting here, Dr. Guerra and Dr. Griffin were here — were present. We have, using the IOM Report on the Future of Public Health, drawn conclusions, specifically, what are the immunization core functions? We have a draft. I would just like to briefly show you what those are. This process will have broad discussion and I'll talk about that in a little bit.

This parallels very much what the functions are in the, as I mentioned, in the IOM Report — the surveillance — and there it covers not only the sea surveillance, but also vaccine safety surveillance and immunization coverage. The second is to outbreak control, and it isn't only just to detect it, but also investigate it and control outbreaks. The third point about informing, educating and empowering people — this is what is apparent and we need to understand, and what people in general need to understand about vaccines and vaccine preventable diseases. It's clear as we move into a different kind of health care delivery system that mobilizing the community, and partners and the participants in the process of identifying health threats and finding solutions to them; it's important and that, the group felt, was an essential function.

Developing policies and plans to support strategies, and in that includes like school entry laws and just planning together, including everyone in the context of partnership to develop immunization plans and actions. Then it's closely related to the next that relates to the rules and regulations that were mentioned in the previous comment. One issue that actually is considered to be critical is how do we link people to health care providers? There was a discussion about the importance of core functions — excuse me — about the importance of including not only immunization, but how are immunizations delivered in the context of a medical home. That is, we want to ensure that every person has access to immunization services. The eighth point is the importance of having providers be current on immunization practices. I think no one knows better than this Committee that every year has a record number of recommendations, and that everyone has to be up-to-date almost on a yearly basis or even more frequent than that.

If we're weighing effectiveness of the quality of services, it's critical. This includes assessing immunization coverage in the doctor's office, but also, are all the standards of practice being implemented in clinics and in doctors' offices? Research is listed here as one that, although it's considered to be a national and perhaps a broad issue, the active research is to be conducted at the local level. So there needs to be some approach for collaboration, some infrastructure that allows the research to be conducted at the local level. The health departments need to participate in that process. Two additional functions were added, and one

is the importance of providing and assuring that vaccine supplies are available everywhere. The last one was suggested by Astra. It's the importance of case management and tracking. This comes from the concern that fewer children are receiving their immunizations in the public clinics and more by other groups, managed care and others. There is a need to ensure that every child is being immunized. How is that quality assurance made?

So this is where we are with the core functions — the processes that we've been circulating very broadly as to all the state and health offices, state epidemiologist partners. We expect to get comments in the course of the next month. Also, we will be visiting a series of states trying to attach some specific costs associated with the activities that go under each of these functions. Hopefully, we will be in a better position to explain and maintain what is that it costs to run state and local immunization programs. I wonder if anyone has a question about this point?

MODLIN: Dave? Barbara?

CORDERO: No?

MODLIN: Okay.

CORDERO: Okay. Then just two quick personnel announcements. March 2nd is an important date. Walt Orenstein will be coming back. He basically is almost done with all the chapters; I've heard there are only two left for the next month. So we're looking forward to having Walt back on March the 2nd. The second announcement is that the other Walt — Walt Williams — has accepted the position of Associate Director for Minority Health, and will be joining the Office of the Director at the beginning of March. I say this with mixed feelings because we're losing our expert in adult immunization, but what better place to be raising and keeping the flag of adult immunization than in the Office of the Director? So thank you.

MODLIN: Thanks, Jose. Next will be an update on the Vaccine Injury Compensation Program — Geoff Evans.

EVANS: Good morning. I have enough trouble with English, so I think I'll just stick with that. I just want to take a couple of minutes and fill you in on an important development with the Compensation Program. Can everyone hear me okay? You should have a copy of the monthly statistic sheet — just a couple of comments on that. The new vaccines that were added to the Program as of this past August — really, it has not been much activity in that area. We have three Hep B claims so far, two varicella and DTaP, which has been covered throughout. There's only one claim filed so far, so I thought that was interesting. Eighty-seven percent of the

retrospective claims have now been adjudicated; the awards amount to $860 million; the trust fund balance is $1.2 billion greater. The 75 cent flat tax that went into effect also in August, which was projected to reduce the revenues about $10 to $15 million, really hasn't done much so far. It seems that there's still a fair amount of money coming in. So there's been some interest in trying to get that even lower. The Advisory Commission on Childhood Vaccines this past December voted a resolution to try to get legislation generated that will reduce that to 25 cents per disease prevented.

I'd like to spend the remainder of my time talking about a recent decision in the U.S. Board of Federal Claims on a condition called tuberous sclerosis. It was a favorable decision for the Secretary involving 22 TSC claims. This reflects the outcome of seven years worth of effort on the part of our office and highlights the importance that we attach to maintaining scientific credibility of the Program, and especially the importance of having a very strong multi-disciplinary expert witness panel, which figured very heavily in this outcome. I think that they have done a remarkable job educating the court on vaccine causation science over the past years. This is particularly important whenever medical issues are grouped together, as was done with chronic arthropathy and rubella vaccines, and it was now done with TS.

Three peer reviewed articles have been generated from the research that was needed in order to basically decide what role, if any, DTP immunization has in TSC. The decision by the Special Master is now being appealed to a judge of the Circuit Court in Federal Claims — excuse me — to the Court of Federal Claims. We expect that that will be appealed further through the Federal Circuit Court of Appeals. In the meantime, I'd like to spend a little time talking about the decision itself and the process. TSC is a congenital disorder that primarily affects the brain causing nodules in the ladder of the walls of the ventricles. Cortical tubers in the cerebrum and cerebellum can also cause growths in the kidney and skin. The cortical tubers that are formed form early in gestation of life and they do not change in number or location post-natally. The best visualization is actually by MRI scanning after 16 to 18 months of age. So there's really no way to look at a neonate or a child under a year of age to really know the extent of the involvement.

It has autosomal dominant inheritance and there's a high spontaneous mutation rate. It often presents with seizures during the first year of life, usually infantile spasms, and there's actually an inverse relationship between the age of onset and the degree of mental disability. Patients with seizures may or may not have mental retardation, but almost always, patients with mental retardation have seizures. Across various studies, the overall prevalence of moderate to severe mental retardation is approximately 50 percent. So this disorder has a consequence. Since

TSC-related spasms can present after a DTP immunization, it's not surprising that DTP is blamed for causing or aggravating a condition. So we receive claims in the Program.
Just as a brief review, there are three ways to obtain compensation. You can either show that an injury listed on the Vaccine Injury Table occurred, and you would be successful unless there is greater evidence of an alternative cause. Much less frequently — only probably just a couple of dozen cases — are cases found compensable based on causation of fact. In the past, this has been thrombocytic — excuse me — hemolytic anemia and GBS in a couple of early cases, but for the most part, most claims involve a table injury. For children that have a pre-existing disorder, then it becomes an issue of significant aggravation, which is what took place in the TSC cases.

Now the Program received a total of 64 claims involving TSC after the 91 large group of cases came in, and over the next few years, many of the off-table cases — over 30 off-table, meaning that they were outside the table time frame — were adjudicated and dismissed. More difficult issues surrounded those that had onset within three days of DTP because the initial Vaccine Injury Table had residual seizure disorder as a condition, and therefore, if they had the onset of seizures within three days, there should be a legal presumption provided them unless there was evidence of a greater cause, alternative cause. Indeed, the first Special Master did find for petitioners and that was appealed, and the Federal Circuit Court of Appeals decided that it was not appropriate on the basis of a table residual seizure disorder, but rather it should be on the basis of significant aggravation. Then HHS began to consider what the possibilities were defending on that proposition.

This was actually the thinking at the time, particularly by some neurologists, such as Dr. Emmanuel Gomez at the Mayo Clinic, who was regarded as the world's authority on TS, and who had testified in one of our cases as a court expert for a set of twins that he was treating. His advice to parents at that time was to withhold the DTP. He wasn't certain that it worsened the condition, but he felt that it was probably prudent to do so. His opinion had a great deal of weight with the court, and the court was really leaning toward finding these on-table cases compensable. About this same time, there was a study that was published, with Dr. Gomez was co-author, which began to shed some light on the relationship between the number of tubers and the clinical outcome. In the interest of time, I'll just say that the study showed that reviewing MRI scans in 75 patients that the ones — the greater number of the patients with greater number of tubers had infantile spasms more frequently, had their first seizure before a year of age, and they also had mental disabilities so there was actually a clinical correlation. These features reflect the degree of cerebral dysfunction caused by the tubers and they

seemed to correlate well with the clinical outcomes, both in terms of seizures and mental disability.

The question then became for us — can the tuber count be used as a predictor of clinical outcome? In working with the Department of Justice, our staff engaged a group of epidemiologists, pediatric neurologists and neuroradiologists to look at this question. I particularly want to give credit to Dr. Marie Mann and Dr. Vito Caserta of our staff. The articles that I mentioned before grew out of this effort. The first paper published was a meta-analysis of five studies published since 1987 of MRIs and clinical outcomes in TSC patients. Dr. Lam and Dr. Goodman, working with three of the authors on the MRI study I just described, analyzed and found both within and across the studies the tuber count correlated strongly with the clinical outcome by seizure status and developmental outcome. Therefore, the cortical tuber count is a reasonable biomarker for predicting the severity of neurologic dysfunction in TSC patients.

The next question was what role, if any, does the vaccine have with respect to infantile spasms since they figure prominently in the presentation, and of course, the reason why a lot of the claims were filed with the Program. As you know, Dr. Belman authored — author of the NCES and co-authored a separate study having to do with DPT and infantile spasms, and in looking at that 1983 paper, it wasn't clear where the TSC patients were. We contacted him and Dr. Lam worked with Dr. Belman, who expressed an interest in this line of inquiry, and this was the result. Basically, they found in doing a separate analysis that the infantile spasms cases classified as previously abnormal were — and those would be the ones that the TSC patients would fall into — there was actually no effect relationship found. In the previously normal, there was a relationship, but it was a recruitment model. Therefore, even though there was a shortening of the time to the onset of seizure, there wasn't an overall increase. So this was further support that there was no causal association whatsoever as far as, not only of spasms, but particularly the TSC cases.

About this time, one of our experts read an abstract in *Epilepsia* that was out of Poland, which described a study of 106 TSC patients looking at immunization. Dr. Joziak was contacted and the result is a paper that's going to be published in the *Archives of Neurology* this March, in which they specifically looked at clinical outcomes and the risk factors, and decided to see if there was any relationship whatsoever with the vaccine. One of the strengths of this particular study is the fact that in Poland, every child has a health book which lists all their immunizations, and is annotated each time they come in and it has some clinical notes. So there was very strong immunization data. In doing a case group control analysis, they found basically that there was a strong association with spasms and there was an independent association with age of onset,

which really reflected the fact that these were spasm onsets. Gender and DTP immunization were not associated at all, so this was even further support for the court.

In the December 15th decision in the two test cases, HHS was found to have successfully shown that TSC is indeed a factor unrelated to the vaccine, and that this is now under appeal. As I said, we expect within a year probably to have a definitive ruling by the Circuit. I would also mention that Dr. Emmanuel Gomez was really a court's expert in this whole exercise. He has since left Mayo; he is retired now, but he does consult with the Program. He has experienced some criticism from the TS community because of this change in thinking. It is my understanding that his new textbook will no longer have that recommendation that DTP will be withheld. He was persuaded by the evidence that was generated with other studies. Thank you.

MODLIN: Interesting. Any questions for Dr. Evans? Comments? Geoff, thanks very much. The next update will be Dr. Rob Breiman, the National Vaccine Program.

BREIMAN: Good morning. As you know, the NVAC focuses on — the National Vaccine Advisory Committee focuses on policy issues. It's our view within the NVPO that NVAC and ACIP should be — their work should be complimentary and mutually supporting. So I thought I would focus my brief update today on the recent National Vaccine Advisory Committee meeting which was on January 12th and 13th. Mimi Glode is the ACIP liaison to the NVAC. We think that that's actually a very important relationship. There actually is not currently an NVAC liaison to the ACIP. It is something that the current Chair of the NVAC, Ed Marcuse, is very interested in and perhaps something we should talk about in the future.

Just to let you know, there have been a couple of recent events that have occurred from the NVAC. There was a publication of a report entitled — actually, I don't know what the title was — but the focus was on the delicate fabric of vaccine innovation, and creativity, and discovery and production. It was published in *Pediatrics*, I think, in January. It focuses on how important the relationship is between public health, and academia and manufacturing in ensuring that we have rapid as possible creation and development of effective and safe vaccines. That is the first step along the way to further identifying what barriers there are to that process and to come up with solutions that would further accelerate the production of safe and effective vaccines. There also has been work that is just about completed now on strategies to sustain immunization coverage. In this period of very high immunization coverage, there are a number of challenges to make certain that this is sustained and anything further improved. So those things are — that's happening and that will be ready for publication soon.

Then I also wanted to point out some of the — very quickly — some of the key highlights from the recent meeting. We had talked about our review and the NVPO of the National Vaccine Plan, and have been in the process of updating that National Vaccine Plan, and will involve the NVAC in that process. As you know, the National Vaccine Plan is a very comprehensive step of goals, and objectives and actions. It was created in 1994 and a lot of things have happened since then. We feel that it needs to be updated and the NVAC wanted to be involved in that. We also discussed our process of unmet needs funding, and developed a plan for how the NVAC could give us their outside non-vested impressions to help us at least set our priorities for funding vaccine research.

We spent a fair bit of time talking about adult issues. One of the highlights that you may be interested in is that the NVAC has been focused on the issue of using non-traditional sites to boost adult immunization, and in fact, held a meeting in December that was very interesting. I have never actually been to a meeting quite like that. It brought people together from all sorts of fascinating walks of life that had something to say about how to get adults immunized, particularly those hard to reach adults that have traditionally been non-accessible. That has led to the development of a report that the NVAC will ultimately put out that will include a number of recommendations for using these non-traditional sites, recognizing that there are limitations, and in fact, there are standards that need to be developed, as well as some evaluation components to determine which efforts are most effective. We also, as you will, spend a fair bit of time talking about influenza, particularly as it relates to what occurred in Hong Kong and how that relates to the issue of pandemic influenza preparedness. Obviously, you'll be talking a lot more about that today.

Also very quickly, the NVAC focused on Welfare reform and how recent Welfare reform has impacted immunization coverage, and what the issues are. In fact, we really just scratched the surface there, and the NVAC will be continuing to examine this potentially important area. We also — the NVPO has been in the process of coordinating the development of a Department of Health and Human Services Vaccine Safety Action Plan, again, a comprehensive approach to ensure the optimal safety of vaccines. We worked out an approach that would again involve the NVAC in various steps along the way. We have also — the NVAC has also been looking at the question of what the impact is of philosophical exemptions on immunization coverage, whether or not there should be a national policy regarding philosophical exemptions. There was a special meeting that was held that also was very interesting. It included, I would say Philosophy 101, regarding the question of the value of independent thinking versus the value of public health, sort of a Hagel

versus, you know, Adam — whoever I'm forgetting — but the key capitalist in our history, Adam Smith.

The conclusion of the NVAC was that there hadn't been thus far a great impact on immunization coverage of and by philosophic exemptions, but that there were major questions that were unanswered that had to do with, number one, why people choose to go that route; what the issues might be related to the potential for risk communication to make certain that all the facts are on the table; that people fully understand both the risk and benefits. Also, it wasn't totally clear what the impact is of philosophic exemptions in local areas. There was some data that was presented that suggested that the focus of several outbreaks, particularly measles outbreaks, was groups of folks that had taken philosophic exemptions. So there clearly were two sides to the story and the NVAC opted for recommendations that were more along the research line. We needed additional information before making conclusions.

Jose didn't mention, but a very important issue that he's working on, and the NIP in general is working on, is the issue of immunization registries. The NVAC will be housing some of the future meetings of experts in the area of computer sciences, and public health and so forth in the process of developing a strategy for bringing along immunization registries quickly. NVAC is very excited about that and is going to be working closely with Jose and his staff on that. Then we also spent a fair bit of time talking about the question of how to make these vaccines that are coming down the pike and have already come down the pike — like Hib conjugate vaccine, rotavirus that we'll be talking about here in the future, and pneumococcal conjugate vaccine things — how to make those vaccines affordable in those parts of the world that actually need them the most. I mean, the greatest impact of rotavirus vaccine clearly would be in developing countries where, you know, it's estimated a million kids die every year as a result of rotavirus diarrhea.

We need to consider proactively over the long haul how we can develop strategies that would encourage the affordable availability of these, you know, critical vaccines in those parts of the world that suffer the greatest impact from those diseases. So we began to scratch that surface. Roy Whittus from the Children's Vaccine Initiative came and presented their perspective. The NVAC expressed a fair bit of interest in developing policies or developing recommendations that could possibly impact policy, including issues related to multi-tier pricing, as well as coming up with strategies that would stimulate vaccine development that would lead to this potential use of vaccines in areas that right now there wouldn't appear to be a great market for. Also, as sort of a related but separate issue is how to make sure that work continues on developing vaccines that would be primarily for use in developing countries like, for instance, malaria vaccine. So those were the highlights. Again, we hope — we had

started the process a while back of considering how ACIP and NVAC could optimally, you know, be symbiotic and mutually supporting. There still is great interest in continuing that and we might want to re-examine how best to do that.

SNIDER: I'd like to add — I don't think there's another place on the agenda for it. This is Dixie Snider for the transcriber. The NVPO and NIP, the FDA, the National Medical Association have been working together for the past year in a dialogue with the Nation of Islam, which has been concerned about vaccine safety. This apparently was precipitated by a book by Leonard Horowitz, but there are other issues that have come up — SB-40 for example — that have raised questions in the minds of people in the Nation of Islam about whether immunizations are as safe as the general public believes and as the medical profession believes. I just want to commend those programs for working very well with the Nation of Islam. There's going to be another meeting this month, I think, on the 20th to discuss these issues. As I said, they continue to come up. Those of you who may have carefully read the *New York Times* article about the discovery of the HIV from the 1959 isolate will maybe have noted some off-hand comments by Dr. Ho about how immunization programs might have contributed to HIV spread. From talking to the people here, I know that seems to be something that's very unlikely.

We've been through the immunization issues before, and I won't outline all the arguments against it, but just the age distribution of AIDS cases and the age distribution of people who get vaccines and so forth, just on the surface, it doesn't match up. My point is that I think it's — we feel it's very important to engage these communities because these are the most vulnerable communities that are being represented here. We certainly don't want anything to happen to those communities and the children in those communities. So it's very important for these programs to work together, I think, and continue the risk communications efforts that they've started. We're very appreciative of the assistance we've gotten from FDA, as well as from the National Medical Association in helping us engage this.

MODLIN: Thanks. Dr. Faggett?

FAGGETT: Okay. Walt Faggett, NMA. I agree with the previous comments. I think the panel on the 20th has an opportunity to give more accurate information to the Nation. I think their request was to get accurate information so they could better inform their population. I think what they're very interested in is how much capacity does CDC and FDA have in terms of regulating vaccine safety. I had a question for Rob relative to the Vaccine Safety Action Plan. Are there any new developments which need to be publicized relative to vaccine safety so that a community like this could be informed of new levels of capacity of the CDC or FDA?

BREIMAN: Of course, the Vaccine Safety Action Plan is going to be about action steps that need to be taken in the future. I think the encouraging thing is that it will include action steps that would even further improve our surveillance for adverse events, as well as to even further improve our ability to detect adventitious agents or contaminants in vaccines and to study what their impact is because the two are not — I mean, a negative effect does not necessarily follow the presence of an adventitous agent in a vaccine. We need to learn more about that. So most of the safety plan really is talking — is recognizing the need and the interest for doing those things and will need to be implemented. It certainly won't, you know, obviously, it won't be implemented by the time of that meeting.

FAGGETT: Okay.

BREIMAN: But it does recognize an interest in doing so.

FAGGETT: Thanks.

MODLIN: Thanks. Fernando.

GUERRA: Fernando Guerra. Rob, seeing your list of the areas that NVAC is interested in pursuing reminds me that the concern about immigration reform and how that is impacting on very significant numbers of people, and within that are some immunization requirements. Is that also under consideration?

BREIMAN: It hasn't been something that's been discussed at the meeting yet. It's something that we've talked about putting on the agenda. I wonder if maybe we should talk a little bit more about how to focus that and what issue — maybe who to involve in, you know, in those discussions.

MODLIN: Thanks for the question. Sam, did you have a comment? Dr. Sam Katz.

KATZ: Sam Katz from Duke University. This may be a moment at which to make a comment of which many of you are already aware, and that is of the Infectious Disease Society of America and the Pediatric Infectious Disease Society — representing most of the physicians who take care of patients with infectious diseases and promulgate preventive programs — have embarked on a program called the *Vaccine Initiative*, which I think focuses on some of the issues we've just been discussing. The co-chairs of this program are Lou Sullivan, the former Secretary of HHS, and myself. We've established an office at Vanderbilt University with Bruce Gallen, who's on leave from Gina Rabinovich's and John La Montagne's program as our staff director.

Our initial survey indicated that despite the best efforts among the public — and particularly, the public we're talking about who may be the disenfranchised indigent public — there's some degree of skepticism

about information that comes from government agencies, as well as some about that which comes from pharmaceutical firms. So that we hope we could build a coalition with a collaboration among all groups to promulgate educational information, not only for parents and for parents to be, but also for providers so they would be prepared in advance to respond to or perhaps to modulate in advance information that was going to appear in the media that might be either incorrect or destructive in various ways. I hope you'll be hearing more from us and I hope that all of you around here will be willing to participate with us.

MODLIN: Thanks, Sam, for that information. I'm going to ask that we move on. Bill — I'm sorry — Paul, did you have something very quick and absolutely necessary?

GLEZEN: Yes. I had a question for Bob and that has to do with the inclusion of high risk patients in immunization registries so that we do a better job of recalling patients for influenza and pneumococcal vaccine. I sense there's a disconnect here because I hear people talk about vaccine preventable diseases, and there are more deaths from varicella than any other vaccine preventable diseases. I think that we need to make sure that influenza and pneumococcus are included in those so that we get better coverage.

MODLIN: I'm sure you'll get no argument from Rob. Did you want to respond?

BREIMAN: Well, I was going to — I nodded to Jose; I didn't have an answer.

CORDERO: I agree that they need to include the issues in terms of the logistics to go from a childhood to a broad, high risk immunization registry are pretty daunting. I think our first step is to start with the children so we can get it started, and show that it works and how it works, but clearly, the expansion and the natural step for expansion is into influenza and to the high risk patients and pneumococcal.

MODLIN: Okay. Thanks, Jose. We're going to spend the rest of the morning and the early part of the afternoon discussing influenza in several different segments. We're going to begin with an update on the H5N1 outbreak in Hong Kong. Dr. Cox and Dr. Fukuda will be leading the discussion; I beg your pardon, Dr. Fukuda.

FUKUDA: Thanks, John. In the next hour, we're going to be talking about the H5 influenza virus and related activities. Because of this cluster of cases, it's really brought a lot of attention onto the pandemic planning process. Because of that, we'd like to have one other person speak after Nancy. Dr. Martin Meltzer will be talking about some economic modeling which is going on for pandemic planning. I think that should be quite — a lot of interest for this Committee here. So what I'm going to do in the next

several minutes is kind of summarize the epidemiologic field investigations that have been done to date on the H5 virus. Can people see this?

So what I'm going to be talking about is basically two field investigations which were done between May and January of this year in Hong Kong. Now rather than put the acknowledgments at the end, I think that anyone who's ever been involved in anything like this realizes you can't do it without the help of a large number of organizations and people working very long hours. These are some of the organizations that were working on this investigation. I'd really like to highlight the efforts of the Hong Kong Department of Health and Department of Agriculture which really did, I think, a heroic job in dealing with these cases. Now to review briefly, influenza A(H5N1) viruses are viruses which have previously been found only among avian species. These have not been known previously to cause disease in humans. Now for those of you that were here at the last ACIP meeting, I think that you remember I updated the group on the first investigation, but to quickly summarize, in May of 1997, a three-year old boy who had no chronic underlying illnesses developed a typical upper respiratory illness with fever, sore throat and cough. He was diagnosed with pharyngitis by his regular physician, and he was given antibiotics and aspirin.

On day six of his illness, he was hospitalized because of continuing high fever. By ten — day ten — his illness had progressed so that he needed to be intubated. On that day, a tracheal aspirate specimen was obtained, and a few days later, the child died. He died primarily because of ARDS, but he had complicating illnesses of Reye's syndrome and multi-organ failure. On the day that he died, an influenza A virus was isolated from his specimen, but it could not be subtyped by the existing reagents. In August of 1997, a few months later, this virus was isolated as an influenza A(H5N1). The initial work was done at the National Influenza Center in Rotterdam, and it was confirmed a few days later at CDC. There was a series of telephone calls that took place, and then the Hong Kong Department of Health invited CDC to assist in an investigation.

Now to quickly summarize that investigation, I'll go over the pertinent questions and the answers at the time. The first question was whether the virus showed any evidence of reassortment. The work done by Sasha Klimov here and others quickly showed that the genes in the original isolate were all avian. The second question was whether the isolate represented a laboratory contaminant. I think this was probably the leading hypothesis among virologists around the world at the time. Again, based on a great deal of epidemiologic and laboratory evidence, we quickly came to the conclusion that this was not a laboratory contaminant, but represented true infection. The next question was whether this virus actually was related to the child's death or was

somehow a commensal organism. After reviewing the child's illness, and talking both with the primary physician, and looking over medical records and so on, we felt that it was highly likely that it was the cause of the child's death. We thought that the clinical course was consistent with a viral pneumonia consistent with influenza. The virus was identified within respiratory cells using IFA, and even though other pathogens were sought, no other pathogens were found that could explain the illness.

The next question that came up was what was the source of the virus. We felt that it was likely to be infected poultry in Hong Kong. We found out that there had been, at that time, one culture confirmed outbreak of influenza A(H5) among poultry on a farm in the new territories part of Hong Kong. Subsequently, we learned there were two other culture confirmed outbreaks. These outbreaks took place between the end of March and the beginning of May, and this was just before the time that the child became ill. Sequence information indicated that the chicken isolates and the isolates from the child were virtually identical. The next question which came up was then how did the child become infected? We still don't know how that occurred. Again, there were some hypotheses about he could've been exposed to poultry or poultry feces, but we don't have definitive information on that. We feel that it probably was direct exposure to either poultry or poultry feces, however.

Now the large overriding public health question at that time was whether there were other cases, perhaps suggestive of the beginning of a pandemic. Surveillance was increased in the area and no other active cases were identified. However, at that time, approximately 2,000 blood samples were collected for serologic testing. These blood samples were collected from contacts of the case, including family members, health care workers, classmates and staff at the school he attended; laboratory workers in a variety of different laboratories that worked with the virus; and then poultry workers, including those from the farm — one of the farms that the culture confirmed outbreak had occurred. In addition, blood samples were collected from a variety of so-called control groups, including healthy blood donors and healthy children who had participated in unrelated vaccine trials. Now at that time, there was no serologic assay available for testing these bloods. That was one of the things which was embarked upon. That work was largely done by Jackie Katz's group here.

So at that time, in summary, we felt that the pandemic potential was relatively low. We thought that this was likely to be an isolated, or at best, an unusual case. However, recognizing that it was a new influenza A subtype appearing in a population, surveillance was increased both in Hong Kong, but also in southern China in the cities of Shenzhen, Guangzhou and Guangdong Province. Then as I mentioned, the work was begun on developing serologic assays to test for antibody to this

virus. On November 25th, the Hong Kong Department of Health notified CDC and indicated that a second case of H5N1 had been identified. The second case occurred in a two-year old boy. This child had an underlying ventricular septum defect and was followed on a regular basis because of that. He developed an upper respiratory illness characterized by fever, and cough and sore throat. He was admitted to a hospital the following day. He was discharged two days later in relatively good health. Now at the time of admission, the child also had a nasal pharyngeal swab taken and an influenza A(H5N1) virus was isolated.

On November 27th, the Hong Kong Department of Health invited CDC for a second investigation. Now the main public health question for the second investigation was really quite focused. The overriding question of importance was whether the new cases increased the likelihood that a pandemic would be appearing. Now in order to answer this question, we broke it down into more operational questions which could be actually answered. The first one that we posed was — is there evidence of increasing human-to-human transmission of this virus? The second question was — was there evidence that the viruses were being transmitted more efficiently now than before? The third question was — was there evidence of either cumulative genetic changes in the virus or was there evidence of reassortment?

To answer these questions, there's really a three-pronged approach to this question. Clearly, there was a lot of laboratory work which went on independent of the epidemiologic investigations, but in the field, there were really two major types of investigations that were done. The first were a series of studies done among humans and the second was a series of studies done among animals — basically trying to map out the animal epidemiology. That work was really spearheaded by Dr. Ken Shortridge and Dr. Rob Webster. Now among the investigations that CDC was directly concerned with was the human investigations. In terms of those, we did the usual kinds of things that epidemiologists do: we conducted case interviews; we went through medical records; we conducted site visits and so on. In terms of the analytic studies, we conducted a series of cohort studies and one case control study. Now the cohort studies were focused on one single question, and that was whether there was evidence of human-to-human transmission of this virus. In conducting these studies, we recognized that the major confounder was likely to be exposure to poultry.

So we conducted about ten different cohort studies and these took place among various groups of people that had had contact or were exposed to the cases. Basically, family members were studied; three different health care worker cohorts were studied; two different school based cohorts were studied; one coworker cohort and one group of recreational tour members that had traveled with one of the cases. In addition, there were

two cohorts: one that was exposed to poultry; one consisted of retail stall workers and the second consisted of the personnel that were involved in the large chicken killing operation. In contrast to the cohort studies, a case control study was conducted. This was really focused primarily on defining whether poultry exposure was a risk, but also to explore for other potential risk factors. This was an extremely difficult study to carry out for a variety of reasons, but basically, for each case there were two to four controls selected. These are randomly selected from the neighborhoods. They were age and sex matched to each of the cases, and we collected one blood specimen from each of the controls to confirm that they were seronegative for H5N1.

Now one of the difficulties of this study is that the interviews necessarily took place with proxies. As you will see from the age distribution, many of the cases were either very young children or they had died. In addition, finding the controls was a very difficult task. So between November 6th and December 28th, there were seventeen cases of H5N1 which were detected. Sixteen of these cases were confirmed by virologic culture; one case was confirmed by serology. The ages of the people ranged from one year to sixty years, and they were proximately evenly distributed between males and females. When you look at the epi curve, you can see that a few of the cases occurred in November, and then there was a kind of peaking of cases somewhere around the mid to latter part of December. You can also see from the graph that on the morning — either the late night of the 28th or the early morning of the 29th was when the chicken culling operations began in Hong Kong.

Now this graph is a little bit hard to see and I apologize, but basically, it indicates that the cases were scattered roughly all over the Hong Kong area. In fact, I think it's extremely difficult to see, but there are little X's in there and they're kind of dotted all over. To make it a little bit clearer, if you divide Hong Kong up into the four major districts of Hong Kong Island, Kowloon and New Territories West and East, you can see that there are cases in all of the major districts of Hong Kong. Now although we don't know the true pathogenicity of this virus, one of the striking things was the mortality associated with cases. Of the eighteen cases that were identified, eight of the cases ended up requiring mechanical ventilation. Of those eight people, six of them died; one person was successfully intubated and one person is still on a ventilator, but is slowly being weaned. So we are hopeful that that person will make it off. That person has been on a ventilator for over two months now.

Now as we sort of drew our cases on the chalkboard in a room, one of the quickly striking things was the mortality pattern associated with this virus. I think that when you divide the people up into those above eighteen and below, or eighteen above and below, you can see that six out of seven people who were eighteen or above were cases died. This

is a remarkably high mortality rate in that age group. You can see that among two of eleven cases in people under eighteen died were much lower, but still a strikingly high mortality rate for influenza.

SNIDER: Keiji, could you put that back up?

FUKUDA: Sure.

SNIDER: It actually says "died or intubated."

FUKUDA: Right.

SNIDER: There were six deaths and I just wondered if there were any deaths at all less than eighteen years.

FUKUDA: Yes. The original, the first child who was the case that died. I can't remember if there's one other case, but at least one case died under eighteen. Now it wasn't some time until the beginning to middle part of the second investigation that we had serology results available from the first investigation. You can see here that when you divide the case — the people who were in close contact with the case — you can see that in general, the seropositivity rate was low: 0 of 4 family members had antibody, 1 or 2 percent of health care workers, less than 1 percent of classmates, and 1 out of 63 or 2 percent of neighbors. Similarly among laboratory workers — and these were people who worked in the veterinary laboratories, the hospital laboratories and the research laboratories — 1 out of 73 workers was seropositive. This didn't contrast to 5 out 29 or 17 percent of poultry workers who showed antibody to H5N1. Again, among 18 swine workers who worked on farms which were immediately proximate to the poultry farms, there were no seropositive workers. Then among approximately 419 controls — both adult blood donors and children in vaccine trials — there were no seropositives.

Now in terms of the cohort studies, when you aggregate them all together, we collected about almost 2,900 questionnaires and approximately 3,300 blood samples. Dr. Katz's group has been furiously working on trying to get the serology results. We're very close to having all of those bloods tested. We hope to have preliminary analysis results available very soon, shorter than two weeks. Similarly for the case control studies, we enrolled 15 cases and 41 controls. We should have results available very shortly. So I'll summarize the epidemiologic investigations and observations at this point.

The first point, I think, we're now a couple of months past the last case and I think that people are beginning to relax, but I think that one point that I want to drive home is that the period between the first case and the second case was six months. So I think we really don't know what this

period means when we're not seeing any cases right now. This is extremely important to remember. The second point is that — and there should be the word "hospitalized" in here — this is an unusual age distribution for hospitalized cases of influenza. As opposed to elderly people that we normally see in the inter-pandemic period, these cases that were hospitalized occurred primarily in children and in young adults. Similarly, the mortality pattern was unusual. It was extremely high for an influenza virus as far as we can tell. The deaths were concentrated primarily among young adults which, I think, for many people raised the spector of the 1918 virus.

Now based on available evidence, both the laboratory evidence — which I did not go over — and the epidemiologic evidence, we believe that there's probably a close link between the avian and human infections which have been detected in Hong Kong. There have been cases in both humans and in birds which have been identified at roughly the same time. The molecular evidence suggests that there's very close linkage between what's going on in birds and what's going on in humans. The serologic results from the case-1 investigation suggest that exposure to poultry was the predominant risk factor for that case, or is one of the predominant risk factors for this infection, rather than exposure to another infected person. Then finally, although we don't really know what the effect of the culling operation has been, it is striking that there have been no additional cases identified since that began.

So at this point, we believe that the transmission is primarily poultry-to-human. We will see what the new cohort and case control studies indicate, but that is what we currently see right now. It also — transmission also appears to be relatively inefficient, as opposed to other types of influenza in which we may expect to see hundreds or thousands of cases appearing over a relatively short time. What we have really seen is a cluster of cases, which is common, and now apparently ended. However, even though the transmission appears to be relatively inefficient, again, I think we have to remember that the second reappearance of this virus has been associated with the cluster of cases as opposed to a single case. The second thing to remember is that these viruses have a propensity to change, and even though we don't see strong evidence for human-to-human transmission, evidence from one of the seropositives suggest that that probably occurs at some low level. This is something that we want to keep on top of.

Then finally, I think we know that no epidemiologic study may give us the answer that we seek, but I think that one of the important things about the series of studies which has been done is that it gives us some baseline information for which we can compare in future studies if this virus reappears, again, particularly to look at whether the kinetics of this virus appear to be changing. So I think I'll stop there.

MODLIN: Thanks, Keiji. If there are very specific questions for Dr. Fukuda regarding the outbreak and its investigation, let's ask them. Stan? Otherwise, I'd prefer to save the general discussion until the end of the hour.

PLOTKIN: Stan Plotkin, Doylestown, Pennsylvania. Is there — I've heard conflicting information about mainland China. Is there any evidence for H5 flu on the mainland? Secondly, do you have any serologic evidence of infection in swine?

FUKUDA: The question to the second one is no as far as I know. Dr. Cox actually went to China as part of the WHO mission, so why don't I let Nancy answer that question or address that one.

COX: As Keiji mentioned, I did participate as part of the WHO mission which traveled to China during January. We were told that there is no evidence for transmission or for the presence of H5N1 viruses currently in the poultry in China. We talked extensively with people from the agricultural sector, as well as people in the Ministry of Health.

I thought we'd start out with a lighter note here. Can you hear me? We've been trying to collect chicken jokes. It's been a fairly intense time in the influenza branch. I'd like to thank everybody in the influenza branch — many of whom are in the audience here — for their extraordinary efforts to keep up with the normal flu situation, as well as carry on with looking at this very important H5N1 problem. I thought I'd go over briefly, although Keiji has already mentioned some of the characteristics of the viruses, the fact that we have actually examined quite a number of these strains that have been isolated from humans. All eight are in A segments of all of the viruses of avian origin.

The hemagglutinin and neuraminidase gene sequences from these human strains are quite similar to those from an isolate obtained from a March poultry outbreak in Hong Kong and other additional isolates as you will see in a minute. One very interesting thing about these viruses is that they have an H-A cleavage site motif, which is characteristic of highly pathogenic avian viruses. All of these human strains that have been tested so far, when put back into chickens, are highly pathogenic and kill the birds in a fairly short period of time. This work has been done in collaboration with colleagues at the Southeast Poultry Research Lab in Athens, Georgia.

There is some variation among all eight gene segments of the first four isolates that we sequenced and subsequent strains that we've sequenced. So we're seeing some variation among the strains, although there are striking similarities among the strains as well. Now important for vaccine strain selection, or in fact, vaccine candidate development, we

have seen that there's antigenic variation among the strains isolated in humans. Rather than show you an H-I table which sometimes is fairly confusing for people, I thought I'd show you a dendergram, which shows the sequence relationships — the evolutionary relationships — among these influenza A(H5N1) hemagglutinins. What we have found is that these viruses have H-A's which are on the Eurasian lineage. There are two very distinct lineages of H5N1 hemagglutinins — one of which circulates in Europe and Asia, and a second which circulates in the Americas. These viruses, as would be expected, are on the Eurasian lineage.

We have these viruses dividing both antigenically and genetically into two groups which we've labeled here and group 1 and group 2. So we can distinguish viruses in group 1 from group 2, both genetically and antigenically with four-fold or greater differences with post-infection ferret serum titers. Now what I want to point out here — and this is fairly important to our understanding of what's going on — is that we have viruses isolated both from chickens, which are indicated by the "CK" before the Hong Kong designation, both in group 2 and here in group 1, as well as human strains in both groups. So it appears to us that the viruses that are appearing in humans reflect the viruses that are circulating in the chicken population. I need to highlight the fact that the sequences, the H-A sequences from the avian strains, have been shared with us by Dr. Rob Webster. There has been a great deal of international collaboration involving multiple groups, such as the World Health Organization, various federal agencies here, as well as members of academia. So in summary, we can just — we have antigenic variation among these strains and what's circulating in humans reflects what's circulating in birds.

We were very interested to look at the level of antibodies to the H5 hemagglutinin in the U.S. population. As you can see in children and young adults, there are no detectable antibodies in using a microneutralization test. So we are interested in developing vaccine candidates that we would have available should the need arise to produce vaccine. We have special consideration for developing these vaccine candidates. First of all, there's the safety consideration. We need to protect our laboratory personnel, as well as the environment, and make sure that this virus doesn't get into the poultry population in the U.S. There are very specific USDA regulations regarding the shipment and use of these viruses. This includes a P3 level containment in the laboratory; P3 plus, which involves the regular P3 requirements plus shower out.

What we're trying to do is take multiple pathways. This work is going on in many labs worldwide. I want to emphasize that this work is not going on only at CDC, but is also being carried on by labs in the U.K., Australia

and a variety of other countries. One approach would be to identify a surrogate A pathogenic avian virus, which could be used safely by the manufacturers. We would be looking for a virus which had similar antigenic properties, but did not have the ability to cause disease in birds or people. Another approach would be to remove the multiple basic amino acid cleavage site in the hemagglutinin, and then using molecular techniques to rescue that H-A back into an appropriate genetic background. Now in any case, our vaccine candidates for the H5, unlike regular vaccine candidates for the human strains that are circulating, will have to be tested for pathogenicity in animal models. Of course, as usual, they will need the growth and processing characteristics that the manufacturers require for successful production of vaccine.

So again, we're looking for a related A pathogenic avian virus. We have explored in some detail this particular candidate, A/duck/Singapore/97, which is an H5N3 strain. It's being worked on in a large variety of labs worldwide to assess its suitability as a candidate. It could then be reassorted with PR/8 as we normally do to make high growth reassortments. In addition, we're looking for other strains that might be even more closely related than the duck/Singapore virus is to these Hong Kong human isolates. As I mentioned, we are also using the approach of modifying the H-A cleavage site and then rescuing the H-A gene back into either a PR/8 background, an A/Ann Arbor background — and this work here is being done at Avaron and we've been in close contact with them — or rescuing it back into an avian background. This particular virus was obtained from Brian Murphy at NIH, and had been extensively characterized and used to make avian human reassortants that were a candidate for live attenuated vaccine strains.

So what kind of progress have we made so far? In our laboratory, we used the H3N2 [A/Aichi/PR/8] reassortant to make a back reassortant with the A Hong Kong/156/97. Now we have an H3N1 reassortant, which is ready for rescue of a modified H-A gene. We've also used the Mallard reassortant — H3N2 reassortant provided by Brian Murphy — and we've got an H3N1, which is also ready for rescue. They'll be used as helper viruses to rescue the modified H-A genes. We're in the process of using site directed mutagenesis to alter this multiple basic amino acid cleavage site. I won't go into detail, but we're using two approaches: one to modify the site such that it reads like an avirulent cleavage site — avian cleavage site — and the other approach would modify it so that it reads like the typical human cleavage site.

So we hope to be able to rescue the modified H5 H-A genes using our 71 reassortants, and to be able to test these candidate vaccines for attenuation in experimental animal models. We are, in addition, continuing to assess the appropriateness of the A/duck/Singapore/97 strain. As I mentioned, we have been collaborating very extensively, as

have many other groups with industry and with other WHO collaborating centers and so on. We collaborated with Protein Sciences to express the H5 H-A of the first isolate, the Hong Kong/156 and baculovirus. In doing so, we provided a PCR product, a full-length H-A, which they have successfully expressed and produced an experimental vaccine. Folks from NIH may wish to say a bit more about this particular vaccine which will be used in safety and immunogenicity trials in the near future. We're also collaborating with others to look at the potential for developing DNA vaccines against these H5 viruses.

I think I'll close here with two discussion questions. These questions were raised at FDA's Vaccines and Related Biological Products Advisory Committee. The Committee had a very, I think, useful discussion of these two questions — mostly centering around the first question — but we would like the Committee to comment on the need for immediate production of H5N1 vaccines for use in developmental clinical trials, and also if possible, some comments on the nature and scope of clinical trials that would be needed to support the licensing of H5N1. Obviously, this is in the purview of FDA, but it's very useful to get comments from experts. So we would appreciate any comments that you might have.

MODLIN: Thanks, Dr. Cox. Did you mention that — is it Dr. Meltzer had a presentation?

COX: Yes.

MODLIN: Okay.

MELTZER: Thank you for your time. I'm going to very briefly present some initial results. Please note that caveat; this is very preliminary. The idea is just to alert the Committee that this work is going on. We invite people — perhaps not right now at the Committee meeting, but certainly afterwards — to please get in contact with me or anybody else regarding these estimates I'm going to present. We'd certainly appreciate and welcome any comments and suggestions as to how to improve the accuracy. This is a list of the guilty parties involved with this work and I intend fully by the end of this — by the time we complete this work to name more names. The final acronym there is a committee that has been tasked — for those who aren't aware of it — for providing some planning for the next influenza pandemic. I suppose because I wasn't fast enough, that committee tasked me to look at some of the economics. I didn't duck fast enough.

As I see the task of looking at the economic impact of the next influenza pandemic, I listed out some basic objectives. First of all, we need a range of estimates of just the numbers of people who will fall ill, the number of people who will require outpatient ambulatory care, the number of people that'll end up in hospitalization, and the number of people who

might die without any deliberate, well-planned intervention. These numbers are needed more in the case of, not the exact estimate, but orders of magnitude so planners fully understand what might happen. Once you have those base numbers, you can then attach a dollar value to that impact. With that dollar impact, you can then begin to look at the economics of various scenarios for an intervention. There might be two extreme ranges that I have hypothesized. At the very smallest type of intervention that you might suggest, is just vaccinate all those deemed at high risk — very similar as I see it to the current ACIP recommendations regarding influenza vaccination in an inter-pandemic period.

At the other extreme, some people might recommend or suggest, "What about vaccinating everybody who moves and even those who don't?" Any other scenario intervention probably falls logically in between those two extremes. One of the questions, but not necessarily the sole question that would decide which scenario you would choose, would be what is the economic consequences of any of those interventions? The methodology that I've adopted here is to — again, I emphasize not to produce a single estimate — but to produce a range to give planners and everybody involved in this process some idea of the orders of magnitude and how certain variables might affect the total impact. Is it the attack rate? Is it the hospitalization rate? What drives the economics associated with an influenza pandemic?

There's, of course, also a great deal of uncertainty about what the next influenza pandemic might do in terms of impact. Nobody can really tell me that the next influenza pandemic is going to create X number of people hospitalized. That kind of crystal ball, unfortunately, does not exist. So in order to allow for this uncertainty, I've used Monte Carlo simulation, which uses probability distribution for important inputs like the rate of hospitalizations within certain age groups. Another point I wished the model to show was what would happen to various important key variables — a line for different ranges and the one-year national crude attack rate. For example, what happened if 15 percent of the U.S. population became clinically ill during the next influenza pandemic — 15 percent of all the people in America? When I say "clinically ill," those are people who have an outcome anywhere from half a day off work to death. So that's clinically ill that manifests in an economically important or recognizable impact.

I also stratified the U.S. population into three age groups as outlined here: 0 to 19 years, 20 to 64 years and 65 years and older. It is possible, of course, to stratify the U.S. population even finer, but I run into problems of data. Although a lot has — influenza has been studied in the pandemics and inter-pandemic periods have been studied extensively over the time, and there's a great deal of literature — finding data that you need to put into an economics model. The number of hospitalizations per age group

in any given year and the differences from year to year in influenza virulence make it very difficult to find the data necessary to divide the age groups even finer. I also stratified the population into two risk groups — what I've labeled "standard" and "high risk." The high risk is those with existing comorbidities or medical conditions that make them a greater risk for the more serious outcomes, particularly hospitalizations and death. This is a little different from the ACIP definition of high risk for the 65 years age group, where essentially, anybody over 65 years of age in the current ACIP recommendations is recommended to have an influenza. I'm talking of people 65 years and older that have a pre-existing medical condition that put them at higher risk than their colleagues 65 years and older of having a serious outcome due to influenza.

I do want to emphasize at this stage that this is not an epidemiological model. To make my model work, I need input regarding the epidemiological parameters — the attack rates and so forth. To get to the results — the initial and preliminary results — estimated deaths starting at a crude attack rate, the national one-year crude attack rate of 15 percent, the mean number of deaths will be just under 100,000. There is, of course, a wide spread between the 95th and 5th percentiles, and even the maximum and minimums. You'll notice as you go over from left to right, as your crude attack rate increases, the difference increases between minimum and maximum. The graph line is spread out even further. However, I think you'll all agree that even at a 15 percent national crude attack rate to allow for approximately 100,000 deaths, represents a significant impact on the U.S. society.

Let us take a little look here at what these deaths might mean. What this table suggests — the first important part I wish to draw your attention to — is that unlike typical death patterns that one sees in the inter-pandemic years, the deaths in a pandemic are likely mostly to accrue to those less than 65 years of age. That's basically — two words can sum up why: baby boomers. The largest bulk of the U.S. population is under 64 years of age. Following previous patterns of pandemics, they will be as at risk, perhaps even more at risk than those older of falling — succumbing fatally to flu. I also wish to point out that those people that we've defined as high risk with a pre-existing medical condition are actually going to bear the bulk of the deaths. The U.S. population does not consist of 76 percent of people with pre-existing conditions, yet 76 percent of the deaths approximately are going to take place amongst those with a pre-existing medical condition. Therefore, from this table alone, we see one obvious scenario in terms of intervention — vaccinate all those at high risk and make that a top, top priority. You don't need — I think everybody would agree — you don't need to put economic dollars on this graph. This table should show it.

There is, of course, around each one of these numbers a distribution in terms of probabilities of the numbers involved. For example, 65 years and older, the 95th percentile is about 55 percent. So again, these are not absolute predictions. These are just means of a range of possibilities of what might happen. In terms of hospitalizations, which can carry an enormous economic burden if somebody has to be in the hospital on an artificial ventilator, we see the numbers can range from about 300,000 right up to over 1 million depending on the crude attack rate and what the virulence of the strain that causes the next influenza pandemic. It is, I think, a worrying message for planners that if the crude attack rate is very high and should the next influenza pandemic be caused by a strain that is rather virulent causing a great number of hospitalizations, do we have the hospital capacity to handle the maximum, the 95th percentiles, and even those maximum ranges? Bearing in mind that it might occur in a relatively short space of time, if it does occur in three to four months, for example, the main bulk of the cases occur in that time period, do we have enough hospital beds?

Finally, I just want to list some numbers regarding the number of people who might require ambulatory or outpatient care, and those requiring what I term "no formal medical care," but require some self-care; those that require anything from a half a day off work up to even two weeks off work and will require some time in bed — somebody else perhaps to help them and who will cause an economic impact. Note the scale on the left hand side. This is no longer thousands as in the two previous graphs, but this is millions. We're talking, at average, the number of outpatients at a 35 percent crude attack rate of over 40 million people requiring ambulatory care. Those requiring no formal medical care but relying only on self-care, again, on the same order of magnitude. The question is, again, do we have enough resources to deal with these kinds of numbers in a very short period of time?

It is these kinds of numbers that I think we want to take to a committee planning what to do for the next influenza pandemic to give them an idea of the order of magnitude of what has to be done, and also to bring forward in terms of funding how much funding is needed for planning, and what should be done perhaps on a year-by-year basis in order to make sure that we are prepared for the next influenza pandemic. That's all. Does anybody have any questions?

MODLIN: Terrific. Thank you, Dr. Meltzer. Are there any questions specifically for Dr. Meltzer? Paul?

GLEZEN: Are we going to have a chance to ask Nancy questions?

MODLIN: Why don't we open it up for at least questions for each of the three presenters, but we do need to get on fairly quickly to discussing the specific points that Dr. Cox raised.

GLEZEN: Well, I'd just like to say that there's been a tremendous amount of work done by CDC in all these areas. I think that they need to be congratulated about that, but I have some specific questions about the potential of H5 to be the agent of the pandemic. Most of this resides around the statement in the paper in *Science* that says that the "hemagglutinin is the major determinant of host range." Because if that's true, that sort of opens up a new Pandora's box as far as I'm concerned. I usually thought of the pandemic virus occurring after reassortment of an avian virus with a human virus, which would give it the potential to spread in humans, but if the hemagglutinin is the major determinant being as mutable as it is, then, you know, what sort of change would be required to convert this avian virus into a very serious human pathogen?

Just to help understand, I have some specific questions about H5 in Asia. At the last meeting, Keiji said that H5 had only been recognized in Asia since 1996. If this is true, were the earliest isolates tested for pathogenicity in poultry and were they as pathogenic as the current viruses, or was there a mutation that occurred such as was documented by Dr. Webster in the United States that showed just by the change of one amino acid in hemagglutinin, the virus changed from one that was not very virulent in chickens to one that was extremely virulent that Dr. Webster calls the "chicken ebola virus?" So I think that we need some understanding of what has really happened over there. Maybe Nancy can answer this.

MELTZER: I'm sure you don't want an economist to answer that question.

COX: Paul, I wish I could answer your question, but I can point out a couple of things that may correct or clarify certain things. We have — maybe we'll have to move this down a little bit — you see the virus that's most closely related to the Hong Kong strain is called goose/Guangdong/96. This virus was isolated during an outbreak in geese in Guangdong Province in 1996. While its H-A is not identical to these H-A's, it's clearly the most closely related H-A that we have, and it does have an identical cleavage site motif. There were other viruses like this duck/Hong Kong/79 strain, H5 strain isolated in Asia. So these aren't the first H5s isolated in Asia; that's the first point.

The second point is that transmissibility and virulence factors are probably multigenic. We have tried to look at specific regions of the H-A of these viruses from humans and compare them to, for example, the receptor binding site, which could be very critical for attachment. We see that for the avian viruses and the human viruses, they're identical to each

other and they're identical to the residues that are in some of these other strains — some of which are pathogenic and some of which are not pathogenic. So what we are perhaps most concerned about, since these strains themselves don't seem to be transmitted very efficiently among humans, is that these strains might find an opportunity to reassort with the currently circulating H3 strains in Hong Kong and South China, or H1s for that matter, but H3s seem to be predominating, and then acquire the ability to be transmitted from human-to-human.

GLEZEN: The other question I have is related to activity of H5 in the western hemisphere now. We went through epidemics in the United States, and then I think a couple of years ago, there were epidemics in Mexico. I wonder about the current activity in poultry.

COX: I'll just put this back up because I think it's informative. The activity that was in Mexico was caused by viruses represented here by this chicken/Helisco/94 strain. So you can see that these viruses are distinct. They're on the North American lineage. These are Eurasian lineages I mentioned before. As I understand it, that particular outbreak is now under control. Some vaccine has been used in the poultry populations, and my understanding is that activity is under control. In addition, there was an H5 outbreak in Italy in recent months. My understanding from European colleagues is that that outbreak was occurring in backyard flocks in Italy. My understanding is it's also under control now.

MODLIN: Thanks. Dr. Plotkin.

PLOTKIN: In thinking about this, it would be useful to know what's the pathogenicity as far as you can tell at the moment of H5 in mammals, even ferrets for example, and certainly it would interesting in other species.

COX: We, of course, needed to produce ferret serum so that we could do parallel studies to those that we would do normally for the human strains. So we have inoculated — intranasally inoculated — a number of ferrets with a number of these strains. While some of the ferrets don't — they get ruffled fur and so on and we did have one ferret die, this is not unusual. For example, H3, human H3 strains also cause similar effects. So we haven't seen that these particular strains are unusually pathogenic in ferrets. Now I know that other animal studies are going on in Dr. Webster's lab and elsewhere, and I'm not sure about the results.

MODLIN: They're obviously pathogenic in humans. Mimi.

GLODE: Mimi Glode. I have two questions. One was — was there amplification in the chicken population at the time of the second group of 17 cases? Were there lots more disease and lots more flocks infected at that time?

COX: There didn't appear to be a lot going on apart from what was going — well, let's start over again. It appears from some studies that are being done by Drs. Shortridge and Webster that H5N1 viruses were fairly common in the poultry, live poultry markets in Hong Kong. I don't believe — and Keiji can correct me if I'm wrong — but I don't believe that there were widespread outbreaks on chicken farms as there had been between March and May of 1997.

FUKUDA: Let me just clarify one thing. The chickens in Hong Kong come from either China or they're grown domestically. The original outbreaks took place on domestic farms in which the chickens are grown. While we were there, there were a number of retail stalls in which chickens were found to have died, and from some of those, they were — H5 was cultured from them. In addition, there are two large, central wholesale markets, and at one of them, chickens were found to be dying and H5 was also cultured out of them. The chickens from that wholesale market had been distributed to a wide number of retail stalls throughout the city. In addition, at the FDA meeting, Dr. Webster stated that all the chickens they had collected from all retail stalls had shown evidence of H5. So even though we didn't see the same kinds of outbreaks, we felt that there was widespread infected chickens throughout the city.

GLODE: My second question is just your opinion regarding — I don't know about these efforts or how hard or difficult it would be to attack this problem through development of a chicken vaccine and then widespread use of that to control the disease. It sounds like that's being done in some countries or it may be possible.

COX: I think other people would be more qualified to answer that question than I am, but certainly in this country, there are efforts underway to develop vaccines and have them available should a problem arise in this country.

MODLIN: Thank you. Let's go on and address the questions that Dr. Cox has raised. I would like to open up the discussion to the full Committee to specifically the issues as to whether or not we need to initiate production of a vaccine for H5N1 virus, and secondly, the issue of clinical trials. Dave, do you want to start?

FLEMING: Dave Fleming. I wonder if you could talk a little bit, Nancy, about in both of these issues the progression of steps that would be required and whether we could get closer to doing this with sort of a modest expenditure of resources, or whether there would be a decision that would be required now that would require a lot of resources to be invested to begin to move in these directions. It seems like we're dealing with a low but not zerous situation. We want to minimize the amount of time between recognition if a pandemic were to occur and availability of vaccines. So can you talk a little bit about the time lines and at what point

it really becomes a resource intensive — resources will be intensively required to move along?

COX: Right. I think that my own perspective on this is that as soon as the second case was identified, we knew that we had to move on vaccine candidate development. So that really doesn't require anything beyond the infrastructure that we have in place. Obviously, the agencies and different groups involved in this have to find the resources to do it, but it really doesn't require a lot of intensive resources. Once you have the vaccine candidate developed, then we have to find a vaccine manufacturer who's actually willing to make a clinical trial lot of vaccine. I think this is where the NIH comes into the picture. Gina may want to. . .

RABINOVICH: I don't know how you would identify what "intensive" is or what your level is. On December 6th when the — it was the 6th or 9th when the reports came of the second case. The NIAID Food Group sort of was created and that day they went into action. We had been working for a number of years with a group that had taken steps towards recombinant approaches — recombinant hemagglutinin approaches — for H1 and H3, and had most recently in collaboration with CDC, been working on a veterinary vaccine. As a result of the second case — your question is in what time frame you need to move; the answer is about two months ago. We immediately moved to put a contract into place to procure pilot lot of vaccine — H5 vaccine for testing in a phase one trial. That IND was submitted in January and we're hoping if all regulatory aspects are met to be moving into the field in two weeks.

Dr. Iacuzio is in the audience. He is our influenza — DIMD Influenza Program Officer, and can identify some of those other steps that had to be taken in collaboration with CDC and FDA to actually be moving into place. I don't know if you have time for him to make a couple of comments, but the time is now. You cannot wait. I think Nancy can identify that.

MODLIN: Sure. Just a couple of very brief comments, yes.

IACUZIO: As Gina said, when NIAID was notified on, you know, December 6th that the additional cases — actually, it was cases three and four; it was the second death — we realized real quickly that we needed to move fast. Apparently, there was — we were lucky in having an existing experience, I should say, with a biotech company that made a recombinant H-A through a baculovirus vector system. We had done clinical studies with an H1 and an H3 vaccine a few years back, and a few of these studies were published recently. We also, through our repository, on December 9th, shipped out 600 vials of the anti-serum to an A turn South Africa/61 H5N1, which was shipped to the CDC to be used in the WHO diagnostic

kits to the U.S. collaborating centers and to the state and local health departments for surveillance.

We also initiated a contract with Protein Sciences to prepare recombinant H-A, which was sent as a reagent for diagnostic testing. While some of that was shipped to the USDA to immunize sheep to begin the anti-serum production for H5 if need be for vaccine production, material was also shipped to colleagues at NIBFC in the U.K. for similar anti-serum production. The other reagents were sent to, of course, our collaborators and scientists who were working with H5 — Rob Webster, in particular, and our colleagues here at CDC. In talking with Rob Webster, we also acted very quickly through urgent and compelling needs, supplemented his existing grant so he could go to China, work with Ken Shortridge to study the epidemiology on this flu in the animal population to supplement what the CDC was conducting.

The other areas that we worked on was to work with Protein Sciences to prepare a GMP-grade material that could be used in a clinical study. Like Gina said, the contract was awarded ten days after we met on December 9th. The material has gone to — past our reviewers; I should say the protocol has past our IRB review January 5th and was submitted to the — the protocol was submitted to the FDA at Siebert January 13th. We plan to start clinical studies — I'm getting a look from Gina — maybe next week. There are five clinical sites in the U.S.: laboratory workers, FDA, CDC, USDA, St. Jude's — or Rob Webster's group — and also AIMS-Iowa, and possibly two international science — Hong Kong and the U.K.

MODLIN: Thank you. Yes, Rob.

BREIMAN: I might've understood David Fleming's question a little bit differently. If I'm wrong, this may still be a good question, and that is it seems to me that at least the common prevailing feeling is that if we have a pandemic that would be related to this H5 strain, that we would likely use a more conventional vaccine approach using an inactivated H5-type vaccine. I thought that you were asking, but maybe not, what resources are needed? In order to answer question one, you sort of have to get an idea of what the — of how that would help in a way to get us there. Should we, you know — should we eventually, but very rapidly need such a vaccine, and would it help in somehow minimizing the ultimate, you know, resource allocation or at least get over barriers that you would rather identify early rather than during the time of crisis? So I guess what I'm asking is do you think that, or how do you think going ahead and developing using a more standard and activated technique, an H5N1 vaccine now and going through clinical trials might help us should we, you know, down the road actually end up needing it?

COX: Right. I think that provides good clarification. The H5 vaccine produced by Protein Sciences is really an excellent experimental vaccine, or it's an excellent opportunity to look at it in an experimental setting. Unfortunately, they would not be able to gear up to produce the millions of doses that would be needed should a pandemic occur. So we would have to rely on the current inactivated vaccine manufacturers. That was primarily what developing vaccine candidates for that process is primarily what I was talking about. If we go ahead and have trials done that look at dosing and the need for one dose, two doses or more doses to provide a good immune response, we will be far ahead of the game should these viruses begin to spread further. So I think that the resources required at this point in time are modest compared to the resources that would be required should the virus begin to spread. It's my own personal perspective that it would be very, very much worthwhile to go ahead and do these rather modest clinical trials. They would teach us a lot about this particular strain and some things may be generalizable to other subtypes, so it would be extremely useful to go ahead and do these experiments.

MODLIN: Thank you. We need to go on and focus specifically on the question of whether or not the Committee feels that immediate production would be a desirable thing — immediate production of vaccine. Let me take two more comments and questions, and then we really need to get to the bottom of this. Neal and Gina.

HALSEY: Just a comment and then a — or two comments I guess. One, having lived through an immunization division, the swine flu epidemic in 1976/ 1977 and all of the problems, one of the most important lessons that those of us that were in the division at the time took home, and the people who were responsible for that program, is the need for very careful sequential decision-making instead of trying to make all of the decisions ahead of time. You haven't really mapped out that. I recognize the real problem of how much lead time the manufacturers really need, even once they have a candidate vaccine, which makes that very problematic. I think it would be very educational for this Committee to see that. I mean, it's very problematic, but you don't have to make every decision right away, but it's almost on a monthly basis you're reviewing what would need to be done.

I think the most important comment I'd like to make is I sense a feeling that children might be put aside as being secondary as has happened so many times in the development of both new vaccines and in drugs. There is an effort to try to prevent that with regard to drugs. There's a major effort FDA has undertaken and we are working with them from the Academy of Pediatrics to try to get rid of the problem of products being licensed for adults, but then not really licensed for use in children. You presented the data on the lower mortality rate and the regulatory rate

required for children under eighteen as compared to over eighteen. Well, it was only two out of eleven or 20 percent dying or being on ventilators. I would hold that that still is a major problem and I would not want to see this whole process move forward with vaccines that might be made available and ready, but the target would be people over eighteen.

Somehow, I would appreciate an effort being made to look at what could be done in terms of parallel testing of vaccines in children, as well as adults, rather than sequential which is the usual process. Maybe Gina or others could outline that situation. I realize we may not be at the decision points, you know, for use of vaccines in this next year, but it may be the following year or three years from now. We somehow need to avoid the situation where we would have products available only on a limited scale, and then they would be used only in adults and I don't think that would be proper.

MODLIN: Okay. Thanks. Gina.

RABINOVICH: If I could make a number — two comments. I think it's important to keep those factors in mind as we move sort of in a sequential process forward. We obviously have been very interested in the development and evaluation of influenza vaccines in children. To come back to the question that Nancy is asking though, I think it's a relevant question, especially to answer question number one. I don't know if Nancy — based on the extensive discussions that the Advisory Committee or the manufacturers here can comment — what is the national capacity, either private or public, to manufacture pilot lots assuming any of the alternative strategies towards a more conventional influenza vaccine can be created to create a pilot lot to go ahead with the clinical testing because that involves use of facilities which are right now manufacturing flu vaccine for the following season; an expanded but limited number of avian flocks that are required; and the concern about contamination of existing manufacturing facilities.

MODLIN: Nancy, can you answer that?

COX: I think what I — I know that Ron Levendowski has made some preliminary inquiries and Carolyn may wish to comment.

HARDEGREE: Well, I think that one of the things that we heard at our advisory committee, the manufacturers went over the time line. Maybe Dr. Vernon may want to comment for Pharma. However, it is important for people to recognize that even for next year's conventional flu, there is — people are beginning to think about ordering the eggs now for next year's formulation, so there's a very large lead time. I think that the slide that was shown by the manufacturers indicates that somewhere around 20 — I mean, 80 million doses of influenza vaccine were distributed over the last

couple of years and there's a question about whether the capacity has been reached. One of the manufacturers commented that that might be their capacity. That includes the total influenza production by conventional methodology. The willingness of manufacturers and the ability of manufacturers to participate is something only they will be able to address.

MODLIN: Gina's question is specifically the issue of the possibility of the manufacturers producing pilot lots. . .

RABINOVICH: The pilot lots.

MODLIN: . . .pilot lots production. Carolyn, can you address that?

HARDEGREE: No, that's what I'm saying.

MODLIN: No? Okay.

HARDEGREE: Only the manufacturers would be able to address their abilities to and willingness to participate in making pilot lots with one of these reassortments.

MODLIN: Okay.

COX: I think from what Roland had told me very informally, there might be interest by a couple of companies.

MODLIN: Okay. We do need to achieve some closure here because the time's going on — running out, has run out for that matter. Let me ask specifically the members of the Committee if there are any members of the Committee that feel strongly about this issue — have a strong opinion one way or the other, but particularly, if there are members of the Committee that feel that it is important to initiate production of H5N1 vaccines as soon as possible. Anyone who feels that way?

RABINOVICH: I'm not sure this question can be answered at this point in the discussion. I wonder if it should be reserved because it's really important. It's really going to guide national policy and activities by a number — and to put that answer to that question between us and the bathroom may be unfair to the group.

MODLIN: Okay; fair enough. Well, I think — I get the sense that the silence is telling. Carolyn?

HARDEGREE: I think when this question was posed to our committee, it was not to make large quantities for stockpiling or anything like that. It was to make production for using the pilot studies to do clinical studies to get some information, as Nancy said, about dosing, et cetera.

MODLIN: And the response of your committee?

HARDEGREE: Was positive; move forward.

MODLIN: You know, certainly speaking for myself, I would concur that there's no question that this seems to be an important priority. I suspect that the other members of the Committee would feel the same. With respect to question number two as well, in terms of initiating clinical trials and the scope of these trials, I think we've already discussed these issues to some fair degree. Paul?

GLEZEN: Gina raised the question about resources for these trials. I was under the understanding that the pandemic preparedness plan, that the ultimate result of that would be increase in resources to carry out these sorts of studies. Is this plan not on the way to Congress or something? I mean, that's — I think that's a very critical question at this juncture.

RABINOVICH: Well, we do have capacity within existing vaccine, and it's both NIH and others to conduct studies that are required in the short term. In terms of the status of the pandemic flu plan, I think Rob Breiman can comment.

BREIMAN: What is — this is Rob Breiman — what is happening with the pandemic plan is to go into — I mean, there is basically a conceptual plan, as you know, that lays out the issues and highlights areas that need further development partially as a result of the increased heightened interest and awareness following Hong Kong — the outbreak in Hong Kong. There now is an accelerated the effort to get those, you know, those subplans, if you will, completed. With that completion, it would also become a — it would be available a more clear understanding of what the resources would be needed. One of the things that we've been encouraged to do by some members of the working group is to recognize the ultimate cost or potential cost of a pandemic, which is why what Martin presented a moment ago is so important so that one can start thinking in terms of almost underwriting, or think of pandemic preparedness as sort of an insurance policy. When you consider the ultimate cost of a pandemic and the likelihood that would occur some time in the next twenty years or forty years — and in this case, now may be sooner — then the fairly substantial resources that would be required for pandemic — inter-pandemic use and preparedness don't seem really that great. So a lot of this is ongoing, but it is accelerated.

MODLIN: Okay. Thank you. I detect enough squirming in the room. I think we really ought to stop here. Let's take a break. Let's be back at ten minutes past, then we'll continue on.

Could I ask people to please take their seats so we can start up again? Please, can I ask people to please take their seats again so that we can resume? We have a quorum.

SNIDER: While we're waiting for people to get seated back in the room, because I had thought that perhaps everyone yesterday was sitting around watching television as I was — and many people here at CDC — but some of the questions I've gotten in the break, I realize that not everyone is aware that we have a new Surgeon General, Assistant Secretary for Health. Took a vote on Dr. Satcher yesterday; had to have a vote for closure of the discussion which passed as, I think, 73 to 35. Then his nomination passed 63 to 30 — 63 to 35. No, it was 75 to 23 and then 63 to 35 in favor. So his swearing in at the White House is scheduled for Friday. So we're all very happy for him and, of course, sorry for CDC to lose him, and it will create some new issues for us in trying to get our work done here at CDC temporarily without a director, but I just wanted to make sure everybody was aware of that.

MODLIN: Thanks. Bill, you've got to say it; go ahead.

SHAFFNER: Hi. As a fellow Nashvillian, sure I have to say it.

MODLIN: Okay.

SHAFFNER: I'd like to pick up on what Dixie said. We're indeed all very happy for him and I would like to suggest that the Committee send him a note of our enthusiastic congratulations.

MODLIN: That's a terrific suggestion. Will do; thank you. Let's continue on. The next presentation will be on an update on surveillance on influenza activity, both in the United States and worldwide. We'll continue with Dr. Cox. I'm sorry; again, same mistake — Dr. Fukuda.

FUKUDA: Recognizing we're behind, I'll be very brief. I'll take about three or four minutes to go over this. On your agenda, I just want to note that Nancy Arden in the afternoon will be going over the proposed wording changes to the ACIP recommendations. Very briefly, I think most of you know how CDC conducts influenza surveillance, but essentially, we collect information from sentinel physicians on influenza-like illness. We collect estimates of influenza activity from state epidemiologists. We collect information on isolates and receive isolates from a variety of WHO labs in the country — WHO collaborating labs. Then finally, we collect mortality data from 122 cities.

For the 1997/1998 season, the sentinel physicians began reporting increased levels of influenza-like activity some time in November, but this really went above the baseline level of about 3 percent toward the end of December. The baseline level is about 3 percent and it went above that

in week 53. These two maps represent the current level of activity as reported by the state epidemiologists. The red states indicate widespread activity and the green states represent regional activity — sorry, the yellow states represent regional activity. Basically, as of the last report, 45 states in the country are reporting either widespread or regional activity, which is an extremely high number of states.

Now in terms of the viruses which are being reported, as of the most recent report which is week 4 — the end of January — approximately 41,000 respiratory specimens have been collected and tested. Of these, about 8 percent or about 4,600 specimens are positive for influenza. Of that 4,600, about 980 or 1,000 have been subtyped. By far, the predominant subtype has been influenza A and influenza A(H3N2). I think that about four viruses have been identified as influenza A(H1N1) in this country, and ten viruses have been influenza B. The remainder have been influenza A(H3N2). Of those H3N2 viruses, approximately 72 have been further antigenically characterized, and currently, 39 percent of those are influenza of the Wuhan type — the type which is in the current vaccine. About 61 percent is the Sidney, which is the variant — the new variant.

This is the familiar pneumonia and influenza mortality curve. This part represents the expected number of deaths in the absence of an influenza epidemic. You can see that for this year, again, we have peaks. We have gone above the baseline of a threshold, which is about 7.2 percent. P&I deaths increased in the first week — increased above the baseline in the first week of this year and it peaked at about 9 percent a week ago. This week, it's down to about 8.6 percent. We'll see whether that downward trend continues or whether it goes up again.

COX: I'll also go through my presentation fairly quickly in the interest of time. I'm going to be talking about global influenza surveillance. As you know, we have to be tracking influenza viruses globally in order to pick up the new variants which might cause epidemics in the U.S. in the following year. Let's concentrate on the bottom part of this rather busy slide, which shows the level of activity caused by influenza B viruses globally. We see that there have been sporadic isolations of influenza B viruses in North America, and Europe and Asia during this — the last four months. All of the viruses that have been characterized so far are B/Beijing/184-like that is like the current vaccine strain, and there is not antigenic variation. If we look back to the previous six months, we can see that there have been viruses isolated in Asia which are "Victoria-like." I'll clarify that comment in just a moment.

I'll clarify it by showing you this dendergram which shows the evolutionary relationships among the hemagglutinins of influenza B viruses. We very clearly have two distinct lineages circulating: one, the B/Victoria-like

strains and the second, which is represented by our current vaccine candidate. These strains have been isolated only in Asia, while these have been circulating worldwide. Over the past few years, we've been keeping a very close track of where the influenza B /Victoria-like strains have been detected. You can see that we have isolates from Japan, a variety of sites in China, Taiwan and Singapore. Now this picture really has not changed over the past few years.

I'm moving on now to influenza A(H1N1) viruses, and again, we'll concentrate on the bottom part of our table. During the last four months, since October 1997, we've seen a limited amount of influenza activity attributable to H1N1 strains. This has occurred in the U.S., Canada, Europe and Asia. It's interesting to see that we have two kinds of strains that have been detected during the last four months: the Bayerin-like strains, which are represented in our current vaccine, and also Beijing/262-like strains, which have now been detected in Europe and in South Africa. Both genetically and antigenically, these two groups of influenza A(H1N1) viruses that I mentioned are very easy to distinguish. Here we have the Bayerin-like strain and here's our current — the strain that's actually in the current vaccine, and in the bottom showing red, we have the Beijing/262-like or "deletion mutant" strains that had been detected only in Asia, and now we've seen strains in Africa, and I mentioned in France as well. If we look at what's happened with the distribution of this Beijing/262-like variant, — deletion mutant variant — we see that now we have detected this variant in France, Senegal and Johannesburg. There may be an isolate that's from a travel-related case in California. We're waiting to confirm that in the next couple of days.

Now moving on the H2N2 viruses — and as Keiji just mentioned, H3N2 viruses are causing a lot of problems in the United States in terms of epidemic activity. They're also circulating in Canada, and to a lesser extent in Europe; however, they're causing outbreaks in schools. We also have a number of isolates from Asia and know that there's considerable activity being caused there. We have both Wuhan-like that is vaccine-like, and Sidney-like that is variant-like viruses isolated everywhere that they're circulating. I just reproduced a table from the MMWR to show you that we can very clearly distinguish the Wuhan or the vaccine-like strains from the Sidney-like strains here. So here we have recent isolates from Canada and Hawaii, which are Sidney-like. They react well with the Sidney anti-serum, but are not well inhibited anti-serum to the Wuhan and Nanchang strains. The Sidney strains were first detected in Australia and New Zealand in June of 1997, and have subsequently been detected in a wide variety of states in the U.S., and a number of countries in Europe, and a number of countries in Asia.

We have done additional molecular analysis. This just shows you how the proportion of Sidney-like viruses, as determined by RFLP analysis,

has increased during the current period October to January 1998 versus the period April to September 1997. So we can see that the Sidney strains are now predominating when we look worldwide. So now I'll just summarize the status of global surveillance for influenza and the status of vaccine strain selection. Influenza B viruses have been detected relatively infrequently, and activity attributable to these viruses has occurred at low levels over the past four months. Antigenic variation has not been detected among viruses related to the vaccine strain, and B/Victoria strains have continued to circulate only in Asia as they have for the past few years. Therefore, FDA's VRBPAC has recommended that the B/Beijing-like component, which in our vaccine is B/Harbin/794, be retained in the vaccine for next season.

Influenza A(H1N1) viruses have been detected relatively infrequently also, and the activity attributable to these viruses has occurred at relatively low levels in the past four months. However, viruses related to the deletion mutant reference strain, A/Beijing/262, which is not represented in the current vaccine, have been detected outside Asia in Senegal, South Africa, France, and possibly California during the past six months. Therefore, FDA's VRBPAC has recommended deferral of the decision on this vaccine component while additional data are being collected. The story for influenza H3N2 viruses is a bit more complete because we've had a lot more viruses to look at. These viruses have continued to circulate widely and cause outbreaks and epidemics. A new antigenic variant represented by the Sidney reference strain was detected among viruses isolated in Australia, New Zealand in June and July 1997, and subsequently, viruses similar to this reference strain have been detected in Asia, North America, South America and Europe. Therefore, FDA's VRBPAC has made a provisional — and I emphasize provisional — recommendation that an A/Sidney-like strain be included in the influenza vaccine for the 1998/1999 season. Additional data are being collected and analyzed before a final decision will be made in March. Thank you.

MODLIN: Thank you. Could I ask how long — what time period one might have; how long a decision can be deferred from a practical standpoint?

COX: The vaccine manufacturers require that they have one strain to work with at the end of January, and so they have the B/Beijing/184 strain to work with. They would like to have a second strain as soon as possible, and require that they have all three strains by about the end of March.

MODLIN: Thanks. Questions? Paul?

GLEZEN: I have a couple of comments and questions about the current surveillance in the United States. One is that the last weekly report said that "only 21 percent of influenza A viruses had been subtyped." If my recollection is correct, that's way down from earlier. I thought that

previously WHO labs, almost 100 percent were subtyped in previous years, or I'm talking about over the last five years. In view of our efforts to increase surveillance for new influenza A subtypes, this doesn't bode very well for our current surveillance. I know that Bill Shaffner and members of the Committee of the IDSA, Public Health and Preventive Medicine Committee, have been concerned about reduced efforts in flu surveillance by public health labs — state labs particularly. I think this is reflected in the fact that very few viruses are currently being subtyped. I know we've had problems in Texas with this decreased surveillance and decreased subtyping. It seems to me that this is something that needs to be bolstered. I'm not talking about CDC; I'm talking about the labs that report in the CDC — their isolates.

The other thing I think that should be noted — and maybe should be included in this year's recommendations — is the fact that we're seeing severe excess mortality in consecutive years caused by the same influenza subtype. I don't think — my recollection is that we haven't seen that since 1974 to 1976. To me, this is very alarming. I think it just emphasizes the importance of trying to improve coverage with influenza vaccine because we're going in the wrong direction. We know that population factors like increased aging population and increased population density are mediating toward more severe influenza epidemics. To me, this is alarming to see serious epidemics caused by H3 in consecutive years.

MODLIN: Dr. Cox, did you want to respond?

COX: I can respond to the first part of Paul's comment. We realize that there are problems that have arisen because of resource issues in the state health departments. So it has been increasingly apparent that the information that we get is of a lesser quality because the influenza isolates that they do have are not subtyped, or if they are, they're not subtyped in a timely manner. Because H5N1 arose in Hong Kong, we have made a concerted effort to encourage the laboratories to subtype their strains because unless they subtype them, there's no way that they're going to know that they have an H5N1 strain. So we recognize this as a problem; we're looking for resources to devote to this and we hope that we can work closely with the states to improve the situation. I think with regard to your second comment, it is clear that H3N2 viruses are incredibly adaptable and resilient, and that they have caused excess mortality in subsequent years. This is a problem that we recognize and there clearly is a need for improved influenza vaccines to attack this problem.

MODLIN: Thank you. Chinh?

LE: John, I think part of your answer, Paul, is the fault of the clinicians as well. Speaking for my own group at Kaiser Permanente in northern California, most of the clinicians have been sending IFA tests on the respiratory secretions sputum, epi and so on, because the clinical value is so good, you know. A day or two later, you get your diagnosis. So many of the specimens were not sent for viral cultures at all. I think if we were to really look into subtyping and so on for further vaccine composition, we really need to encourage the clinicians to send viral cultures and not IFAs.

MODLIN: That's a good point. The IFA test, in most hands, is actually less sensitive than culture. So it has the advantage of giving you a rapid result, but it is less sensitive and has a major disadvantage, of course, in not having an isolate, and actually, also is very expensive because of the reagents so that — don't want to get off on a tangent here — but in our hospital, we actually encourage culture for that reason, unless there's a reason that you have to know right away.

LE: But in terms of cost, you know, if you sent two tests for the clinicians, sometimes the value of, let's say, studying amantadine or something would be more valuable to send a rapid diagnostic test, but then you have to do two tests to get your cultures, and that in terms of cost control, physicians are discouraged to do their cultures.

MODLIN: Yeah. Thanks. Yes, Pierce.

GARDNER: I thought I'd ask Nancy, the current rule on vaccine doesn't seem to have been particularly helpful against the Sidney. Do you have the option next year to actually include two types of H3N2 and forget about, say, the H1N1? That doesn't seem to be much of a problem in the data that you presented. Can you only pick one type of H3N2 or do you have the option if most of the problem is that? Can you give two types of that?

COX: This is a question that really impinges a lot on FDA activities. I think that having a tetravalent vaccine has been discussed in the past. I think that the general feeling is that the vaccine manufacturers would have to sacrifice a certain number of doses in order to make a vaccine with four components rather than three, and that there would be the need for some additional clinical studies to be done to look for side effects.

GARDNER: My question is still keeping the three components, but leaving out. . .

COX: Oh, leaving out one of the. . .

GARDNER: . . .either an H151 or a B if it doesn't seem to be an issue.

COX: I think that, yeah — we've had those discussions before at the VRBPAC meeting. We have always — and fairly extensive discussions in some

cases — and we have always come to the conclusion that because there are high risk children involved and because influenza is very unpredictable, we really do want to cover the strains that are circulating globally. Certainly with the H1N1, showing the kind of variation that it is at the moment, I think it would be rather dangerous to drop it out.

MODLIN: Other questions or comments? Fernando.

GUERRA: Nancy, I noticed in your map of the global distribution that there was very little reporting activity from Mexico and Central America. Is that because there is considerable lag time or there is not a system in place for being able to track influenza?

COX: That's a good question. We are working fairly closely with our colleagues from the south to improve influenza surveillance. Until relatively recently, Mexico really didn't have a system in place for isolating influenza viruses. Now there's some very excellent people working there, and we're getting more information and a few more viruses to look at from them. Central America doesn't, in general, do very much work. There are certain countries in South America where influence of vaccine is being used on a regular basis, and of course, they have improved surveillance rather dramatically over the past few years so that they know what's going on.

MODLIN: Thanks. Further questions or comments on surveillance? If not, let's move on to the next presentation, which will be given by Robert Chen pertaining to potential changes in the influenza statement regarding Guillain-Barré Syndrome as an adverse event. Bob?

CHEN: Thank you, John. This morning — if I could have the house lights down please — we're going to cover the final analysis of the University of Maryland study results which were presented in a preliminary form a year ago. We will then look at some similarities and differences with past influenza studies. Could we have the house lights down please? We will then look at a risk benefit analysis for one of the age groups that Hector Izurieta prepared, and then look at some of the language issues focusing on the 45 to 64-year old. There was some discussion earlier as to whether we should shorten the language. The feeling was that perhaps it was a bit too lengthy and that it may kind of overly alarmed folks. On the other side, the feeling was — some of the other folks felt that this is a controversial topic and the length is needed to explain the issues, and that in that sense, it's really only one page in the MMWR. In the past, when other similar topics — for example, whole cell pertussis — we have gone as long as, I think, three or four pages.

So moving on then, next please — as many of you know, back in 1993/ 1994, we detected an increase in reports to VAERS, more or less can double the baseline and even after some adjustment for doses and

timing, et cetera, the signal was still there. So then we went on to conduct a validation study — next overhead — with these investigators at the University of Maryland headed by Paul Stolley's group, and then at CDC involving Larry Schonberger, as well as folks in my group. In that sense, we conducted a retrospective case cohort study. We focused on four states, adult population, totaling about 21 million population, who had statewide hospital discharge data sets available. IRB gave us approval to conduct the studies. We focused on kind of two periods — 1993 to 1994 flu season, as well as the control season from the previous year. We looked at the flu vaccination coverage for the two seasons via a random digit dial-in survey in the four states conducted in July and August of 1994. So about slightly less than one year for that season and then slightly over a year for the previous season.

Ascertainment of all cases — house-wise cases — was based on hospital discharge data. We then requested hospital charts, reviewed the charts, abstracted them using standardized data collection form, classified them according to definite probable and possible. Then we ascertained the exposure history of the GBS cases, first by obtaining permission from them to contact their physicians and then validating it. The analysis was based on the definite and probable cases only. I should mention that the analysis in general attempted to come up with a conservative estimate. Of these, we were able to reach 70 percent of them for interview.

Of the 180, 116 did not report any influenza vaccination; 32 reported receipt outside of our predefined six-week risk period; 19 confirmed receipt within the six weeks; 6 reported influenza of vaccination, but the doctors were not accessible because they moved or because permission was not granted. So based on kind of the distribution in other cases, we imputed 2 out of those 6 as exposed; 7 reported influenza vaccination, however, the doctors were unable to confirm and we deleted these seven — excluded these seven from analysis. Next.

So then the results of crude analysis shows a relative risk of 2.41, statistically significant when you adjust for age group and the year comes down a bit. In terms of the specific years of one season alone, it turns out the control season was statistically significant. Then as many of you know, in the 1990/1991 study, we found a higher risk in the younger folks 18 to 64 compared to 65, but this time, we found basically similar, however, a kind of subgroup analysis of this younger age group did find a potentially — or did find a higher relative risk. In terms of distribution of onset intervals, there was a non-random clustering with a peak during the second week, and the P value on this was .009. In terms of the pre-existing kind of — or kind of antecedent illnesses in the swine flu situation, there was evidence of kind of a substitution effect of the vaccine for other illness. Here, we found that the vaccinated cases in general had lower

prevalence of antecedent illness compared to non-vaccine associated cases though the P values were not statistically significant.

Then in terms of the background incidence of GBS, what we found was that there was a striking difference that we had always thought as rare an illness as GBS was, but in general, all studies have done basically just a single point prevalence. What we found was that in our studies that, in fact, there was a marked increase of background GBS between the 1992/1993 and 1993/1994 seasons, essentially almost a doubling of background rates of GBS. Next. Then in terms of the two seasons, there was also an increase in coverage between 1992/1993, 1993/1994 on the order of about 5 to 10 percent depending on the age group. Next. So then in conclusion, the signal that we found in VAERS, in fact, was really due to an increasing combination of several factors: increase in the background in GBS incidence, increase in flu vaccine coverage, but actually not increasing the risk of the vaccine, per se. So this was actually somewhat of a surprising finding, but overall in terms of the GBS with flu vaccine itself, we did find this 1.83 elevated risk with supporting evidence for causal association, including the non-random distribution, as well as this potential substitution effect.

The attributable risk when calculated turned out to be about one to two cases per million doses, definitely on the margin of what epi methods could define. We did find in one season alone that — our control season — it was statistically significant. Now in retrospect, it turns out that this order relative risk was generally similar to other control studies since 1976. Next overhead and we'll kind of come back to this one. As many of you know, in the immediate post-swine flu seasons by Hurwitz and Kaplan, they conducted studies which found a point estimate in the 1.4 range for two of the seasons though non-statistically significant. Our 1990/1991 study, when you aggregate these together, there was also this non-statistically slight elevation and a separate breakdown.

So one possibility was that earlier studies were also finding something similar, but just that their power — their sample size was inadequate. Next overhead. In fact, when you — the next one — when, in fact, you plot the onset intervals of these different control studies and if you even exclude the Maryland study in red, you see that in general there does seem to be this kind of deficit of cases in the first week, and kind of increase in cases in the second week. Again, the numbers are very small so it's hard to make real heads or tails, but it's at least suggestive of one explanation as to why this may not have necessarily been found earlier. Going back to the overhead that — and then so this issue of whether this 45 to 64-year old elevated risk that we found in this study, and let's go back; okay, then move on ahead then. In the 1990/1991 study, which is the other kind of recently done control study, if we break down the 18 to 64 age group, which was statistically significant into the 18 to 44 and

45/64, we did not find this difference in age as we did in the recent study though, again, the numbers are very, very small. So these are very wobbly estimates. Next, yes.

So then we decided to look at the only source of large data that we have and that is the VAERS data. What we did here just to explain is that we took the new cases into different age groups from VAERS by season, and then for the denominator, we took data from the National Health Interview Survey, which did have estimates of age group specific coverage. Then based on the 1990 census, we imputed approximately how many people in each of these age groups would have gotten vaccinated, and then just did a simple Chi square comparing this kind of two-by-two table against the 65 plus. In general, when you take all the seasons and the patterns are relatively similar, comparing 18 to 64 to 65, there's really nothing remarkable per se. Next overhead.

Then if we take the younger age group and stratify it, and again, comparing it to the older group, there does seem to be this relative deficit of cases in the younger age group, 18 to 44 compared to 65 plus, but then — next overhead — for the 45 to 64-year old compared to 65 plus, there does seem to be kind of a relative increase. Again, kind of the deficit plus the increase, in general, explains why the 18 to 64 overall compared to 65 plus, there was nothing there. Next overhead. Then the one concern, of course, with VAERS data is kind of different reporting biases. So the GBS data is what we just looked at in here. Just summarizing across was what the comparisons against the 65 plus age group data shows. Then we said, "Well, what happens if you just take all reports after influenza vaccination? Do you see the similar distribution?" In fact, we did not see that similar distribution. Then we also asked the question, "What happened if you just take all neurologic reports after influenza vaccination to VAERS excluding GBS? Do you also see this pattern?" Again, we do not think that we see that pattern. Next overhead.

So in general with VAERS, there has been a lot of question as to what its value has been. This is a different study that was presented here several years ago where we were interested in the question of the risk of seizures following DTP doses 1 to 3 versus doses 4. These were different estimated rates coming from passive surveillance, MSAEFI and VAERS, and then kind of the risk ratios across that. Then we went to our active surveillance data with the large link databases, and definitely found much higher rates as one would expect with the active to passive reporting ratio of — ascertaining ratio of about four — but what's interesting was that the basic signal was essentially retained. So VAERS, despite its problems in general, there are certain signals that one would not necessarily discard.

So coming to the next overhead then — this is in too small print to read, but in the mail-out to you ahead of time, this was available to you and I think it's also available in the back. Hector Izurieta did a very nice analysis. Let's just move it up to look at the summary and looking at the excess P&I hospitalization rates for persons in this age group in terms of whether they had medical conditions at high risk for influenza complication or do not have, and then giving us kind of estimates per 100,000, and again, given that our attributable risk estimates for the GBS is kind of five to ten times less frequent than this in terms of 1 to 2 per million or kind of .1, .2 per 100,000. This is useful data for constructing the draft language which we will go to next.

So in — let's see; if we kind of move it down a little bit, we're — no, I'm sorry, the other way, yeah. So we kind of highlight that the evidence for causal relationship of GBS with vaccines prepared from virus strains since 1976 is definitely less clear. Again, in the 1976 situation, Larry Schonberger, et al. had the advantage of, I think, several hundred cases of GBS. In all virus studies, we're dealing with a much smaller sample size. We highlight how obtaining a strong evidence for a possible small increase is very difficult for a rare condition like GBS with a low background rate. In last year's statement, we said that — we kind of identified five or six seasons studied since 1976 — the point estimate was slightly elevated; however, none of these studies was the overall elevation significant. This is now inaccurate with the final analysis of the Maryland study, which showed one of the two seasons that this study was significant. So we kind of rephrased this one to stop in 1991, and then go on to talk about the most recent season, and then the final relative risk figures, pointing out that the number of GBS cases peaked two weeks after vaccination.

The statement last year also kind of was more or less kind of left over from the 1990/1991 statement, kind of highlighting the difference in the older age group compared to the younger age group. Again, this is now inaccurate because the Maryland study did not find this difference at least in terms of these age groupings. So the three options then are to delete the sentence completely and make no mention of the age difference. Another is to kind of more or less maintain the same wording and just to substitute 45 for 18 to 64; to substitute it and make it just 45 to 64. This is kind of an indirect way of hinting at this potential risk, and so then option three is to make it a more active form saying that "data suggest that if an increase relative risk does exist, it may be higher for persons 45 to 64."

So then the only other real substantive change then is in the next paragraph, which is on the next overhead, where in the statement last year, we said that since we do not have the attributable risk yet at that time, we gave kind of a general statement that even if GBS was a true side effect in subsequent years, the estimated risk for GBS was much

lower than 1 to 100,000 found in the swine flu. So now that we do have this estimate, we put that in there. Then with the amino analysis by Hector, we also put in information that is much more specific on the benefits of influenza vaccination for this age group. So that's all I have in terms of presentation, and the discussion really revolves around whether we want to make any kind of age group distinction or not, and if we don't have the first part, then this latter part here may not be necessary either.

MODLIN: Thanks, Bob. Before we open up the discussion, I'd like to ask Fernando as Chair of the Influenza Working Group whether or not you want to summarize whatever discussion the working group has had so far. I know you're continuing to meet on this issue.

GUERRA: The working group that met yesterday pretty much developed a consensus around this revised statement, leaning pretty much towards option three. That seemed to probably be the cleanest of the three options in terms of really focusing in on the issue of the relative risk that does exist, and perhaps it's higher for that age group of 45 to 64. The other thing that was also discussed in the instance of wanting to try to replicate the kind of study that was done by the University of Maryland that it would be a formidable undertaking and at a very high cost. So this is probably the best information that we have access to.

MODLIN: Thank you. I would like to open this up completely for both questions and discussion on the issue, and then we will try to take a vote on this just prior to breaking for lunch. We'll start with Marie and we'll go around the table.

GRIFFIN: I have three comments. One is we saw preliminary drafts of the paper and a number of us were concerned that a lot of issues weren't addressed. I haven't — have other people seen the updated draft?

CHEN: We did not pass that out, but we do have a draft that has cleared CDC clearance, and if you like, we could pass that out to the members.

GRIFFIN: Because I feel a little uncomfortable about not being able to assess the possibility of information bias and some of the other issues that we discussed at the last working group meeting. The second is the age differences. I'm just — the confidence intervals are so wide. Are there statistically significant differences between the age groups?

CHEN: All the VAERS ones are clear because the large numbers are, in terms of the — no, but let's see; yeah, all. . .

GRIFFIN: No, I mean based on the University of Maryland study.

CHEN: Yeah. That one is the summary — no, no, way back — but it was, yeah; the comparison in terms of that specific age group was.

GRIFFIN: Right. One point estimate was statistically significant, but I doubt if the differences between the point estimates were very different.

CHEN: Yeah. No, I don't think we. . .

GRIFFIN: I just think it's making a lot of a very little bit of data and especially when you're talking about risks in the range of 1 per million to say that the risk is higher in one age group, but I think that's really stretching it. My final comment is I think — I applaud you for looking at rates of influenza disease. I think it points to the fact that it's not in the rest of the influenza document. I think we should be able to look back into the influenza document and be able to figure out what the risk benefits are. So I would make a plea to putting the incidence of disease — excess disease, excess hospitalizations, as well as excess deaths which are there — putting those estimates in the body of the document and not just in this section on adverse events because I think those are data that physicians need and patients need to decide whether to take the flu vaccine in the first place. I think that they're not there. So now that you've done this work, I would encourage that to be put into the body of the rest of the document.

MODLIN: Thanks. Chinh?

LE: Yes, I have two questions, Bob. Number one, do we know the risk of Guillain-Barré Syndrome after natural influenza illness?

CHEN: Yeah. We did not look at it in this specific study, but multiple other researchers have. It turns out that they're not associated, per se, in the studies that have looked at the issue, but as you saw, not only a number of other infections, Campylobacter and other viral infections have.

LE: In the hand-out that you have on Table 2, there were 61 cases of Guillain-Barré, not vaccines associated, which have respiratory symptoms and other respiratory infections. I wonder whether you were specifically looking for influenza.

CHEN: Yeah. Unfortunately, these were kind of just by history. They really did not work them up further as to what respiratory illnesses they had.

LE: Then there's no data in the pediatric age group.

CHEN: That's correct. In part, the studies — I guess, in part, the signals have really been in the older age groups. The number of VAERS reports of GBS in the pediatric population have been very small.

MODLIN: Thanks. Rich?

CLOVER: With regard to that same table, you compared background illnesses in those patients who got GBS. Did you compare background illnesses in those who received the vaccine and got GBS versus those who received the vaccine, but did not get GBS?

CHEN: Did they receive the vaccine but did not — no, because those who received the vaccine and did not get GBS was studied under random digit dial-in survey. So it was a different data source compared to the cases. So we did not have that information available.

MODLIN: Dr. Nichol.

NICHOL: I applaud your efforts to include information on absolute risk, as well as relative risk in this statement as we struggle with how to be honest but not overplay a very tiny absolute risk if it's real. I wonder if I might request consideration of two changes to the wording or else I could give it to you later.

MODLIN: Sure.

NICHOL: I'll go ahead. The first paragraph, the last sentence — "six weeks following vaccination was 1.83 representing 1 to 2 cases per million persons vaccinated," again, throwing in the absolute risk there. Then the second to the last paragraph starting with the second sentence — "even if GBS were a true side effect in subsequent years, the estimated risk for GBS was .1 to .2 cases per 100,000 vaccinations. Rates which are only 10 percent to 20 percent of those observed following 1976." Skip a sentence or actually the next sentence — "the possible risk for GBS is substantially less than that for severe influenza, which could be prevented by vaccination. This is true not only for persons aged 65 years and over, as well as those who have medical indications, but also for persons 45 to 64 years of age," and then give the estimates. I'm just pleading for a stronger statement about benefit.

CHEN: Sure, and that is just one question. The thought from the working group yesterday was that instead of shifting denominators between 100,000 and one million, that we would just stay with the 100,000 and change the numerators. Do people have a strong feeling with that?

MODLIN: No. Okay. I think keeping the same denominators makes a lot of sense. Alright, Carolyn.

HARDEGREE: Some of my colleagues have raised the question about why the sentence that's in bold print in the first paragraph in the — near the end of the paragraph that combines 1992 and 1993 with the 1993/1994 seasons has

been done to give the overall, as opposed to stating that in one of the years, there was a significant difference observed as you've shown in Table 1, but it was not statistically significant in 1992/1993. Having said that, whether or not the exclusions and the probable versus proven causes — of proven cases of Guillain-Barré were the same in each of those age — or each of those years. Where there are differences, we haven't seen the papers as Marie has indicated. So was there anything different about the inclusion of cases?

CHEN: The distribution of definitely the definite and the probables were similar between the two seasons in terms of the six or seven exclusions. I don't have that right off, but we could check that to see how different they are. In terms of highlighting the general season, one or the other, it is a possibility. I guess, in general, the feeling of the investigators was that it really was more of a question of power that, in general, all the other characteristics of the distributions, et cetera, between the two seasons were otherwise very similar so that while it may be technically true that only one of the seasons was statistically significant, it would be perhaps kind of discarding data that otherwise is consistent with the Association.

MODLIN: More comments? Neal.

HALSEY: In terms of risk communication, I think it's easier to digest 1 per million than 0.1 to 0.2 per 100,000. I just wonder if you wouldn't just stay with 1 per million. Marie said it; it was easier for me to digest. The second thing is in that modified sentence on the second page that reads — it's about beginning four lines down — "the possible risk for GBS is substantially less than that for severe influenza which could be prevented by vaccination." When I first read that, I thought, "Boy, then the risk of severe influenza for causing GBS is much higher than that for the vaccine." I think that should be reworded just to indicate that it's substantially less than the risk of serious complications from influenza to distinguish those.

CHEN: Okay.

MODLIN: Good point. Dave.

FEDSON: David Fedson.

MODLIN: I'm sorry; we've got two Davids here.

FEDSON: I beg your pardon; I'm sorry.

MODLIN: Dave Fedson, go ahead, and then Dave Fleming.

FEDSON: The guy in the inner circle should come first, I think.

MODLIN: No, you're standing already. We won't make you get up again; go ahead.

FEDSON: Thank you. You're very kind. I can stand longer if you wish. I'm concerned about the ascertainment of vaccination status in both cases in controls in your study. With such an increase in influenza vaccine use in the United States — the doubling of use, for example between the years 1991 and 1996, and all of the attention that is being given by many groups, including the National Vaccine Advisory Committee to the delivery of vaccines in non-traditional sources — I just wonder how reliable going from a patient to a doctor's record is in ascertaining the vaccination status of any individual case or control. I mean, people get vaccinated in their grocery stores, down at the fire station, in senior centers. Did you look into what happens in the fire stations, and the senior centers and the grocery stores in terms of determining vaccination status? Can you really rely on the ascertainment data on vaccination status in these studies?

CHEN: Well, I think that's a good point, David. I don't know if Walt Williams is here. He's the — and maybe Ray can comment on this. The previous studies in terms of validating personal histories of influenza vaccination compared to actual chart reviews, in general, turn out to be kind of 90 percent plus that it is not a thing that, you know, if you're mentally competent, it happens once a year. It's a special effort, a special decision that is required on your part. So it's not a thing that, in general, most people have great difficulty in recalling, but yeah; it ultimately, unless we had an adult immunization registry, I think it will be hard to be able to convince the skeptics.

FEDSON: Did you base your analysis then on just the verbal report from the patient alone and conduct that sort of analysis, or did you base it on the MD/physician validated form?

CHEN: As I mentioned, we, in fact, bent over backwards and actually on the exposed cases, even if the patient reported that they were vaccinated and we were not able to obtain a physician verification, those cases were excluded. Whereas, on the random digit dial-in surveys, since we did not have the resources to verify every single one of them, we accepted their report of vaccination. So in general, that type of differential kind of misclassification bias would result in a bias towards null — towards not finding an association. So in general, we actually did something to bias ourselves against finding an association.

MODLIN: Alright. Dave Fleming.

FLEMING: As a number of people have said, including you, Bob, this study is probably on the margin of where epidemiology has the ability to show that there's a risk. In that context, I would favor some sort of mention of that

fact in presentation of these study results. Currently, the last part of the first paragraph that reads as a statement of fact, I would — while there is some acknowledgment of limitations earlier on, I think to be fair to the reader, we need to acknowledge specifically with respect to the study that there are some limitations that should interpret the readers — should help the reader to interpret these findings as opposed to just a straight statement of fact.

CHEN: I think that's a very good point.

FLEMING: When we get to this discussion around age specific issues, I think I agree with Marie that we're probably maybe past the place where epidemiology can really help us there. In addition, I have some real concerns for our primary audiences at the state and local level; how they would operationalize these kinds of statements related to age specific risks given all of the problems that we know are inherent. I would favor just being silent on that.

MODLIN: Okay. Paul, you were next.

GLEZEN: In relation to questions about vaccination history, in the telephone survey, did the respondent give data only for themselves or did they give it for the household?

CHEN: They were giving it for themselves for the past season and then the season before that — not for the whole household either.

GLEZEN: Not for anybody else? Okay.

CHEN: Yeah.

GLEZEN: But do we know about the mechanics of this, you know — how many houses were called, and how many responded, and how many refused to respond and things like that?

CHEN: We have that in a report, yes, from the. . .

GLEZEN: Because, you know, with marginal relative risk like this, you know, the difference in the denominator could change the statistical analysis pretty easily.

CHEN: We have looked at, yeah — we have actually looked at that very carefully in both the 1990/1991 and the more recent study. It turns out that the primary influence is less the denominator where you actually could live by almost a plus or minus 20 percent.

GLEZEN: For the statement itself, I would make a suggestion that, you know, people have a lot of trouble dealing with probabilities and what they really

mean, but I think that if we looked at, say, the number of cases of Guillain-Barré that might be attributable to vaccine — not just the total number of cases of vaccine associated, the number that might be attributable — and compare that, say, to the number of excess deaths and to the number of hospitalizations that occurred during those same years, that might be a lot more meaningful to people that have to make a decision. The other thing is when I asked a couple of my colleagues in the flu center to look at this, they said, "Well, there's no conclusion at the end of this paragraph." In other words, I think the Committee has to come down and say what you recommend, you know, in the light of this information. That's not clear in there.

MODLIN: Okay. Dave Fedson.

FEDSON: I just have — from a clinical point of view, a physician and the patient will probably want to know not only does GBS occur with a certain frequency following vaccination, but what is the probability of dying of GBS as opposed to having a hospital stay for several weeks; it might be difficult, but then experiencing a full recovery because I think what you need to do is not simply talk about cases of GBS, but I think you ought to talk about cases of GBS versus cases of hospitalization for influenza with survival, say, and mortality from influenza as opposed to mortality from GBS because that's the bottom line. People will probably be much more willing to put up with a 1 to 2 out of a million risk of being hospitalized from GBS, but they'll survive and live a long and happy life, but might be very reluctant to do so if they will die. So I think those mortality rates. . .

MODLIN: Now we're talking about expanding the statement more and more here. Do you think it's necessary?

FEDSON: Well, no, but I'm talking about trying to get something that is clinically cogent so people will have a basis, and whether you die of a vaccine preventable disease or die of a vaccination complication is, for most individuals and physicians, the bottom line.

MODLIN: Okay. Are there other opinions about the issue that Dr. Fedson raised from this Committee? Okay.

CHEN: There's a 5.5 percent fatality rate in this study.

MODLIN: Okay. Perhaps that could be added as a clause to a sentence with respect to the impact of GBS. Yes, Chuck.

HELMS: I believe that a recommendation here is missing from this particular document at the end. I think that some sort of statement about what we think ought to happen is in there. I think we say it in the last very long sentence, but I think the actual decision, which is we believe that people

should receive — people who've had GBS should receive this vaccine, but that maybe with certain individuals, you want to hold back.

MODLIN: It seems to me — I agree; it seems to me the comparative data, the comparison with morbidity of influenza and ultimately mortality tends to make the statement for the Committee, but I agree also that perhaps having a finisher sentence would be a desirable thing to do. I'm going to ask that during the break that Bob, maybe you and Fernando could work together to craft some language that we could take a quick vote on right after lunch without any further discussion or with a minimum of additional discussion. What perhaps we should do would be to take a single vote on the overall statement, and then if necessary, we can take a separate vote on the various options regarding separating out the age groups if necessary. Let's break now; we will come back at 1:15 as scheduled on the agenda. We'll take up this issue right at the very beginning.

Two quick reminders before we start. Before we start, I want to make sure that Bob Chen was right behind me a minute ago. Bob, can you get started even without your hand-outs for the moment? Wait one second. Two quick reminders — one that for those of you who are planning on attending dinner tonight, you need to get your form and your money to the back table as soon as possible, preferably right now. Secondly, again, the usual reminder, that we're having some problems with the tape in picking up conversation, so if you would speak directly into the microphone, and again, make every effort to identify yourself before you begin to speak. We have a quorum so we'll go ahead and get started. We'll finish up with the portion of the influenza statement regarding Guillain-Barré Syndrome that we had asked Bob and his colleagues to revise and present to us.

CHEN: The copy of it is actually being made, so please scribble on your version that you have for now. What I've done is put it in italics and I guess — could we have the house lights turned down, please? I've added in italics the position — it was suggested that we edit the attributable risk language to be added to that paragraph. In terms of the age specific issue, there were about two craftings of them. One was to delete the statement on the age specific. The other one, I rephrased it to kind of take the most firm data. So in fact, two of the control studies — the 1990/1991, as well as the most recent study — actually did suggest that the folks who were older had a lower risk than the younger persons. Then I caveated to say that these results are based on small numbers, however. So that is a factual statement based on the control data if you choose to say something about that. On this part, the changes state that it's one to two cases per million. We had earlier data and we need to find some information on mortality for the youngest age group, and then a concluding statement about that — the benefits of influenza vaccination

therefore clearly outweigh the potential deaths and associated risks for all age groups. That was another suggestion for a statement.

VERNON: You can't say it is "all age groups" because you don't have data for all age group.

CHEN: Okay. So maybe just stop it before the "all age groups."

MODLIN: Further questions, comments, important ones? What I'd like to do would be to actually take two votes by the voting members of the Committee. One would be to accept the overall changes here, and then we'll take a second vote specifically regarding the options for the age specific issue. We have a couple of options that Bob has presented here. Those in favor of making the changes that are proposed minus the option issue? All those in favor of the voting members of the Committee? Nine. I understand that Jessie Sherrod has now joined us. Can we hear her? Why don't you find out if she was able to — if she can't, we do have nine votes in favor. So we'll find out what her vote was soon.

Okay. Moving on quickly to the issue — we have two options now that Bob proposed for the last sentence in the first paragraph. The options are either to delete that completely or to include, or substitute it with the following: "Two of these control studies suggest that if an increased relative risk does exist, it is lower for persons aged 65 years or greater than for younger persons. These results are based on small numbers." Marie.

GRIFFIN: I would vote to delete it. I'd just like to remind people that if they want to include it, relative risk does not represent absolute risk, and that with the increased risk of elderly people, we don't really know what the attributable risk is, which is much more important for the individual patient. So I think that's misleading even if the relative risk were lower in elderly people. It didn't mean — would not mean that their absolute rate would be lower.

MODLIN: Okay. Any other comments? Those in favor of option 1, which is to delete the sentence completely? It looks to be eight out of nine. Those in favor of option 2? Dr. Helms. Have we gotten Jessie Sherrod linked up yet? I guess not. So let the vote currently stand at 8 to 1 in favor of option 1. Dave?

FLEMING: One point that I'd just like you all to consider is at least when I read that change about the vaccine associated mortality rate on the second page, to me, that was a little bit stronger than maybe what we want to say. I think people will read that as, in fact, Guillain-Barré in those folks was associated with the vaccine. In other words, the vaccine was causing the disease. Do we want to say a word — some words that are different, like

"mortality rate in people with GBS who received influenza vaccine was no different" or "it was 6 percent?"

MODLIN: My own view is we're kind of splitting hairs there, but how do others feel about it? Yeah.

RABINOVICH: Sorry, we can't hear you.

FLEMING: Well, my specific concern is five lines down approximately — "6 percent of the vaccine associated GBS cases died." To me, as a practitioner, that says that we're saying that all of the cases were —it implies a causal connection. That's probably Jessie. I'm thinking this may be the telephone connection with Los Angeles; that is what we're hearing.

MODLIN: Dr. Sherrod, can you hear us? We do have a problem with the PA system. Let's continue on while we get that sorted out.

FLEMING: Okay.

MODLIN: Does the microphone sound better now?
GRIFFIN: Yeah.

MODLIN: Okay. Dave, why don't you propose. . .

FLEMING: It's a small point.

MODLIN: Okay.

FLEMING: But my concern is on the fifth line down when you say "6 percent of the vaccine associated GBS cases died." To me, that implies a stronger causal link than what we had previously said in the statement. I would propose an alternate wording about — that says, "approximately 6 percent of the GBS cases who received influenza vaccine died."

MODLIN: Bob, do you want to — is that acceptable to everyone? Okay, fine. Dr. Schonberger.

SCHONBERGER: What I'm concerned about is whether there's been improvement in the treatment of GBS since that study was done. I had heard that there really wasn't a difference in the vaccine associated GBS than other GBS in terms of their case fatality rate. If that case fatality rate has declined a little bit, I don't know whether that's the exact rate that applied to what the person who's thinking of getting a vaccine now would relate to.

CHEN: The cycle was 5 percent in the 1992/1994 study.

SCHONBERGER: So not significantly change is what you're saying?

MODLIN: Gina?

RABINOVICH: So compared to what in the cases that did not follow influenza vaccination?

CHEN: It's the same.

RABINOVICH: Okay. It should say that it's the same; that there was no difference in the case fatality rate among those who received influenza versus those who did not because this is difficult.

GUERRA: That's a good point and I think we can work that through.

CHEN: Didn't want to make it a huge sentence, but if that's the desired. . .

MODLIN: Okay. Any further — we can manage that it sounds like without any additional voting and discussion. I understand that we do now have Dr. Sherrod on the line. Jessie, can you hear us?

SHERROD: Yes. Good afternoon to everybody.

MODLIN: We can hear you quite well as usual. First of all, we need to ask you to disclose any potential conflicts of interest.

SHERROD: I have no conflicts of interest.

MODLIN: Okay. Were you able to hear the — at least the very recent discussion on the changes in the influenza statement regarding Guillain-Barré Syndrome?

SHERROD: I heard parts of it; part of it I missed, but are you voting now?

MODLIN: We have voted.

SHERROD: Oh, you've already voted?

MODLIN: Yes. We'd be interested in what your vote is, however.

SHERROD: Well, I guess the question was concerning deleting that sentence or substituting. That was one thing that — the one concerning "data suggest that if an increased relative risk does exist, it may be higher for persons 45 to 64 years of age than other age groups."

MODLIN: Right.

SHERROD: Which option did you all go with?

MODLIN: Option 1.

SHERROD: Delete the above sentence completely?

MODLIN: Yes.

SHERROD: Okay. I agree with that.

MODLIN: Good. Thank you very much. Let's continue on with the proposed changes to next year's recommendations to next year's statement that deals — additional changes that will deal largely with the selection of strains for next year's vaccine. Dr. Nancy Arden will make the presentation.

SHERROD: Okay.

ARDEN: There are really not any other major issues in the recommendations this year. You may recall that for a number of years, members have raised issues about wanting some kinds of more global revisions in the recommendations. Some minor revisions in this way have been made from year to year; some were made this past year, but in terms of doing a major reorganization of the recommendations and a major rewrite, which hasn't really been done for about fifteen years now, it made sense to us to do this for the 1999/2000 recommendations for a number of reasons. One of the main reasons is that it's anticipated that the live vaccine will be licensed for that year, and that that in itself will require fairly substantial rethinking of the recommendations, and changes and expansion of the current recommendations.

Another possibility is that there will also be one or two new anti-virals — the neuraminidase inhibitors — that will be further along the way. We expect to be able to start thinking about incorporating those agents also into the recommendations. There has been established an influenza working group. It's chaired by Dr. Guerra. They met yesterday; we met again today at lunch. Plans now are to start with having a fairly intensive two-day meeting of the working group, of representatives from industry. This would start, hopefully, in the late spring with a two-day meeting, possibly extending to three days for some people to work out some of the major issues.

Then there would be follow-up subgroups for different topics. Follow-up meetings are tentatively scheduled into the summer with the goal of having draft recommendations for the — in the late fall, early winter. Presumably also at the June meeting and October meeting, there would

be updates to the Committee on the progress. There would be some kinds of summary of issues covered and opportunities for comment. That having been said, there is still the opportunity for people that feel very strongly to make recommendations or comments about more minor changes that might be incorporated into the recommendations for this season.

NICHOL: I have just a very minor suggestion for consideration. For pages four and seven, I am wondering if the ACIP might consider adding language to this effect when talking about, "in addition, influenza vaccine may be administered to any person who wishes to reduce. . ." Might you include comments "any person aged greater than or equal to six months," just to emphasize that children are included?

ARDEN: Okay. Also on page seven, there is the general population statement.

MODLIN: Paul?

GLEZEN: I have three suggestions — if my mike's on — one is on page two, the second paragraph, when discussing influenza associated deaths, I was going to suggest that something be put in about the current season, the high excess mortality being the consecutive year with H2N2 which, I think, is pretty alarming. There's an indication; I think it flows into the next paragraph where we talk about the number of elderly people increasing and the risk of increased mortality, I think, is high. So that, I mean, I think this is actually occurring. I think it adds immediacy to the statement if we conclude it. I would suggest that we include the excess mortality graph for the last five years in this statement because I think it visually brings it home. At the bottom of that page, I wonder if it's possible to consider changing the year 2000 goal because I think for people over 65, we've already reached the year 2000 goal and it obviously isn't doing the job. We haven't — there's no evidence that we've decreased mortality. If we've already reached the goal two years early, I think we need to push ahead. Something needs to be said about that.

SNIDER: We're working on the 2010 targets now, Paul.

GLEZEN: Yeah, but 2000 — I'm talking about for 2000; 2010, that's way too late.

SNIDER: What I'm saying is 2000 is already over and done with.

GLEZEN: Yeah.

SNIDER: We're working very hard on 2010 objectives at the moment.

GLEZEN: Well, maybe we can amend it and get another goal in there because, you know, it's not having an effect on excess mortality. I don't think we ought

to be held back by, you know, problems for that. The other is on page four. Again, the first full paragraph — I was wondering if there could be a statement in there reflecting the study of Potter, et al. that was in *JID*, 1997, that demonstrated that perhaps greater effectiveness in protecting high risk elderly in facilities can be achieved by immunizing the staff. I think there ought to be greater emphasis on immunizing the staff of these chronic care facilities. I didn't see that paper listed in the references.

ARDEN: It should be in the references now although the references aren't complete. The references you're seeing now are not fully updated.

GLEZEN: Well, it wasn't in the draft that I received.

ARDEN: I don't think it's the practice to cite specific studies in the body of the recommendations. This subject actually came up before and there are already recommendations for vaccination of staff. I think we could probably change the wording to some extent to make this recommendation stronger, or to suggest that there is evidence that this is beneficial.

GLEZEN: Right. Yeah. I think that it could be brought out in the list where you list all the high risk groups too.

ARDEN: Well, residents of long-term care facilities are listed as a high risk group. There's a separate section on vaccination of staff.

GLEZEN: Well unfortunately, this is a study that can't be replicated very easily because most places we can't ethically do this kind of study. So it probably won't be repeated.

MODLIN: I think Paul's point is to at least mention the fact that immunizing staff helps to reduce the risk to nursing home clients is effective. Not all physicians read the entire statement and it is helpful to emphasize that. If you have an opportunity to do so, I think I agree it would be useful. Dixie, did you have a comment?

SNIDER: Well, I agree with you about that. I mean, I think it's relevant because these are not two independent, but inter-dependent events. Just in the second paragraph on page two, 1991 to 1992 is marked out. I assume that something like 1993 to 1994 or something else is supposed to substituted.

ARDEN: Oh, on page two? Yeah. That was an omission. It actually should be 1994 to 1995.

SNIDER: Okay.

MODLIN: Dr. Fedson.

FEDSON: In the general sense, I think it would be useful if you would add to the group where you talk about immunogenicity and efficacy, if you would add the word "effectiveness" because efficacy and effectiveness are quite distinct concepts and most of our current understanding of efficacy is really understanding of clinical effectiveness. I think that we need to use those terms with greater precision. I would also make a plea, now that your list is somewhat incomplete, to include a few more references from European investigators, for example, the work of Fleming and his colleagues on the clinical effectiveness of vaccination in preventing influenza-related mortality in the United Kingdom. These recommendations, I can assure you, are read very closely by public health officials in western Europe and in many other countries throughout the world. I think it would be useful if we could acknowledge the contributions that many people in other countries make to our general knowledge on influenza and its prevention.

MODLIN: Any further suggestions? We have on the agenda here that we need to approve wording for changes for the ACIP influenza recommendation. I don't sense that there's much objection to any of the suggestions that have been made. Dixie, let me ask you as a point of order here. Do we need — actually need to take a vote on next year's statement in addition to what we've voted on with respect to the major changes regarding Guillain-Barré?

SNIDER: No, I don't think so. As you all know, I mean, there are two strains yet to be included in the vaccine, and obviously, that has to be added to it. It goes to the MMWR. We've talked about this before and there's going to be some editing. So I think it's overkill to go to all the — you know, into that much detail.

ARDEN: We make minor changes that don't have to be voted on every year; some because members write after the meeting. Anyone who wants to send in some suggested changes and wording that are the kinds of things that don't require a vote or suggest references, please do so by February 23rd because we do have, even though it's not published until April or even May sometimes, the MMWR likes to have the final draft, start on that very early. So the sooner the better.

MODLIN: Okay. So comments on the influenza statement by February 23rd. Okay. Shall we move on to the next order of business? Dr. Livengood will be discussing resolutions for VFC.

LIVENGOOD: Okay. I'm going to just sit here this time because this is a bit different than the usual type of VFC discussion that we're going to have. I'm sorry to intrude on Dr. Glezen's dream ACIP and turn the discussion away from influenza, but we will do so.

MODLIN: Pardon me. Gloria, would you mind turning the lights up for us? Thank you; appreciate it.

LIVENGOOD: As you recall at the last meeting, we did a consolidated resolution on hepatitis B. As I was preparing that and working with Kevin Malone and others, we found we had to trace back through multiple resolutions to figure out which parts of which ones were currently in effect at that time since many of them had been amended, or replaced or repealed and were in many different locations. We have been hearing from many of our partners, particularly those in the field, that they'd like to have a set of absolutely clean and current resolutions, preferably maintained in an accessible location like on the World Wide Web. So that at any point, they could look and see exactly, rather than having to do archaeology to see which parts of which resolution are where, but they would have a current resolution for each vaccine. Then subsequently as those indications, or age groups or whatever changed that, again, there would be one location where we would go in, change the wording and immediately, there would be notice to other people and they would be available to everyone to access in a central location.

I've been very fortunate that Kim Lane from the Vaccines for Children Program actually made the mistake of volunteering to help in this effort. So she's been working on a couple of sample resolutions, and these are strictly just samples. They're in your book here. I didn't get them out in advance because we were doing them rather late. I have two because they illustrate sightly different points about it. Just if you don't have these, I can get them sent to you shortly. These are being read, not so much for content, but more for the format and are the right types of information there all in one location that we could deal with.

Part of the reason we have two is that we've had two different, basically, sets of problems. We have one for measles, mumps, rubella and one for hepatitis A. We have vaccines in the Vaccines for Children Program that are both recommended sort of universally and for — I'm sure the hepatitis people would object to this — but more sort of special use vaccines, which is represented by hepatitis A. The measles, mumps, rubella is really a more central core one. Also too, as we went through them, we found that sometimes, as in the measles, mumps, rubella one, all we were doing was taking different pieces of different resolutions and putting them all in one location. As in the hepatitis A one, we found that there's never been an actual VFC resolution on what the contraindications to hepatitis A vaccine are. That is an actual requirement of the Vaccines for Children law; that each vaccine have a contraindications part of — as part of the resolution as well.

So sometimes, the preface, or preamble or whatever you want to call this — I call it the introduction — the first paragraph of the resolution will clearly for each of them state what's being done. Is it just consolidating or is it consolidating and doing something also about the resolution? So that as you get these over the next three to six months and begin to look at them, that first paragraph should really indicate to you what is going on with that particular resolution or at least what we intend it to be. Sometimes we find that we have inadvertently changed things as well.

The types of things that we — that are legally required in a VFC resolution are, and we have to put in the previous ones that we're appealing and all, who's eligible, what the recommended schedule would be, dosages and recommended dosage intervals. We've added a separate section on catch-up vaccination because as we did the recommended childhood immunization schedule last year, we realized that there was a lot of misunderstanding, if you will, about catch-up vaccination or accelerated schedules if there is one for that particular thing.

The contraindications and precautions, which for the MMR also includes the infamous table about immune globulin production — I mean, administration in the time interval. As you can see for the MMR one, even a consolidated resolution, trying to take all the pieces together run six pages, but does bring things up to the front like who's eligible, what the schedule is and the doses and recommended intervals in case people don't know, but then additional pieces of it, including some of the legally required ones, are there as well. With hepatitis A, again, the eligible groups, instead of being small like it was for the MMR since MMR is everyone twelve months through age eighteen years is eligible under VFC for an MMR, there's a whole list of the special eligible groups that are eligible for hepatitis A under the Vaccines for Children — the schedule, the dosage and recommended intervals, some catch-up indication and then the contraindications and precautions piece of it.

What I'd like to perhaps have, you know, some of the members and liaisons do is just sort of give us advice. Are we on the right track with this? Is this the type of product that we ought to spend staff time and then ACIP time — both in June and probably October seeing the number of them that would have to be done — in looking at these and making sure? These really aren't being presented for, you know, on line seven, you've misspelled a word, which certainly could be possible. Any time I work on anything, spelling is always a problem. I think just, you know, the format, the order — things like that that potentially, and whether or not you think it's worthwhile that we try to do this. I sort of have just always assumed that it was, but those are the types of things I think we'd like to discuss, rather than necessarily reading them in great detail.

Certainly for the MMR one, you know, I did give the advice just to go ahead and reproduce the table *Immune Globulin Administration and Timing of MMR Vaccine*. It is part of the statement. It is something that we and, I think, the Red Book originally put the table together for us, have spent a lot of time because people call with those questions. It does represent a precaution or a contraindication to administration, which is a legally required element.

MODLIN: Thanks, John. Neal?

HALSEY: From my standpoint, I would applaud the effort to do this, but I would even go one step further. What I think people need is a simple table so they wouldn't have to look — a table that they could put on their wall in the office so they wouldn't have to read through all the text. Of even your refined one, I mean, you've made it much easier, but you could just make a table and that table could be updated or downloaded from the Internet as well, which contains the eligibility, basically, is the most important thing.

GRAYDON: Right. This is Randy Graydon, the Health Care Finance Administration. A lot of the feedback we've got from providers is they're confused about the general schedule versus who's VFC eligible. I think this is very good. I agree with Dr. Halsey. If it could be reduced to something that they could just hold in their hands, it would be wonderful. This is, I think, real helpful, a good effort.

MODLIN: Other comments? Fernando.

GUERRA: I wonder if we should also cross-reference the use of the immune globulin G where, you know, there's a recommendation to postpone measles vaccination. Does that hold true for the other immunizations that we give to young children in the instance where they have received that? The time interval is not quite as long, is it, for the DTaP and polio?

MODLIN: The answer is no. Neal, do you want to expand on that — Fernando's question?

HALSEY: Sorry. We were going on to the next point.

MODLIN: The question was do the guidelines for MMR with respect to use of immune globulin and delaying immunization apply to other live viral vaccines, and it does not.

HALSEY: That's correct. We have some data on rubella from the same study that George Sieber and I did where it had much less effect than it did on measles, and there are no data on varicella vaccine, and there are no

data that we're aware of on mumps vaccine. So you're right, you know. We simply don't know.

MODLIN: And OPV as well.

HALSEY: What we chose to do with varicella is say that we don't know, but if you want some guidelines, use the same ones that you use for measles because we assume that all immunoglobulin products have, you know, varicella antibodies in them. So we've made some guidelines, but they're arbitrary.

MODLIN: Fine.

GUERRA: How about in the instance of the other childhood immunizations, DTaP?

HALSEY: Well, the statement that we issued in the Red Book and the general recommendations on immunization from 1994 all include statements to the effect that immunoglobulins in general do not interfere with the development of antibody responses that will give you protective levels of antibody. High titers of passive antibody will bunt the response, but that's covered in our — in the general recommendations, at least from this Committee.

GUERRA: I just wonder if we shouldn't cross-reference that though because somebody reading this could, you know, perhaps make the assumption that that holds true for some of the others.

MODLIN: Sam?

KATZ: I have a question about number two under the MMR about anaphylactic reactions. "Children should be vaccinated only with caution using published protocols." Are there any published protocols that tell you anything to anticipate? My understanding was that the published protocols showed there was no relation to skin testing or anything else and no anaphylaxis. It seems to me that's a dead horse that's been beaten too long.

MODLIN: That, in fact, was changed in the new MMR statement, which is not yet published. So that is a hold over from the old statement. John, is it not? It's a good point. Thank you, Sam.

LIVENGOOD: Yeah. That's a different point from the list of other stuff. We had a list and we're updating that too as well.

MODLIN: Yes. Thank you. Dixie?

SNIDER: I think the cross-referencing is important to look in thinking about the table, which I fully agree with. Still for legal reasons, we may, John, need to tell people — to refer them to this full document, whether it's going to be on the World Wide Web or whatever because that table is obviously not going to contain everything that is required under VFC. So I don't want us to get into some kind of legal difficulty publishing a document which contains a subset of the VFC information without referring to where all these things are, which leads to my question. Have we already started to figure out where we're going to put this? It seems to me the World Wide Web is a reasonable thing to do.

LIVENGOOD: I didn't talk to any of the people actually with the VFC Program, but certainly we could, you know, put them together in a small pamphlet or publication that could be distributed to people as well. The problem has been that things change and then it's been extremely difficult to change them. That's one of the things I like about the World Wide Web. If we change something like which, you know, one of the contraindications or some new thinking on them, we can just go back and alter the document, and date it that this is the date it's correct, and we can keep a current copy there, everywhere. I agree with you about the table. The table can only be sort of a handy guide to eligibility. It's not the whole VFC resolution itself, but it certainly, you know, we could pull the eligibility out of each one and summarize it down on one sheet of paper. That probably would assuage 90 percent of the calls that we get. I imagine HCFA gets a much larger number of them than we do, but just to, you know, and then refer in that — "for further information, see" — either a document, but it could go, I suppose in the MMWR, but I just find it hard to believe that they want to engage in something.

SNIDER: Well, I mean, I don't want to belabor this, but we have discussed this before about the general recommendations. This is an opportunity for us to think about it again. We don't have to decide today, but clearly as information comes forward, we make changes in our recommendations and, you know, to wait for hard copies to grind through the system, and then to take the risk that people have the wrong version is not the ideal situation. It would be — I think this is a wonderful opportunity with this shorter document to begin to think a little creatively about how to disseminate information in a better way than we're doing it right now. Again, not that we have to discuss, you know, that extensively today, but I think it is an opportunity to begin to use some of the technology that's available to us, and make these changes rather quickly and disseminate the new information rather quickly.

MODLIN: Larry.

PICKERING: Larry Pickering. I think tomorrow we'll hear from the working group on computerization of the ACIP recommendations. If the programmers are

quick, that should be available fairly soon. Jonathan, I think it goes along with your ideas about putting it on the Web and the availability will be there for a greater number of people. That should be able to be moved forward on a fast track.

MODLIN: Great. Thank you. Further comments? Fernando.

GUERRA: Let me go back to the hepatitis. I wonder if it might not be prudent to perhaps make some notation that in the instance where a household member has either hepatitis C or other chronic liver disease, that children within that household and family should be vaccinated against hepatitis A, and that that would certainly be a group covered by VFC given the fact that so many of the children with hepatitis A have a very subclinical infection. If an adult member of that family has hepatitis C, they're certainly at great risk for a more serious problem.

MODLIN: Is that now — let me ask because I don't know — is that now, that seems to be more of an issue for the ACIP statement on Hep A as much or more so than it is for the VFC statement. I have to admit to ignorance. The information about risk of Hep A to patients with Hep C is relatively new information and I doubt that it's contained in the Hep A statement. Tom, you're shaking your head. Is that the case?

VERNON: No. I don't think that's the case.

MODLIN: So it's really, I think, a bigger issue for the next time that we revise the Hep A statement, but it's an important point. It's a very important point and it's something that we probably should address soon with respect to changing it.

SNIDER: But if it raises a generic issue about the approach to this from John's standpoint, and that is whether what we're trying to do at this particular point in time is to codify all the different VFC votes we've had into one coherent document, and then that's really the only purpose of this exercise, or whether in addition to that, we're going to revisit each VFC vote we have taken and, you know, look at the content — not just from the standpoint of whether it's consistent with what we've already voted for under VFC, but whether we still are comfortable with it. I'm not saying one way or another, but it does throw a different perspective on what we would be asking the program to do and what we'd be asking the Committee to do. It would be nice, I think, to get some sense of the Committee about whether in the process of doing all this, you know, questions ought to be raised about whether certain things ought to be changed in light of new information or whatever because I think John would, I mean, we need to charge John with a task that — we need to make the charge clear about whether their task is really to gather

together the information to create a new document or whether to raise issues about potential changes in VFC resolutions.

MODLIN: I think you've heard that there's some considerable enthusiasm for doing so, but go — I'm sorry.

LIVENGOOD: I would agree that we perhaps can do both. I'm a little hesitant to get too far. For example, actually, the first one Kim started doing was OPV. To think of — I mean, polio vaccine, to think of the schedule and everything like that, I was like, "Please pick another one. I've had enough polio considerations for a couple of years." I hope you all keep that in mind too. I think to some extent doing something like writing in the thing whether or not it is just a consolidation of things or identifying are there changes would help the Committee, but it is a different task to then begin to look at each one.

While I think it could be useful and it certainly ought to be done on sort of a routine basis — that we go back and revisit these to think if there are things to change — in general, we've been told not to get the VFC resolutions out in front of the recommendation. Because I think you recall with the hepatitis B one, we actually changed the hepatitis B recommendation. That is in emerging and infectious disease all of its own. That will come out at some point in the future. At the same time, we did the VFC resolution because the VFC resolutions technically can't be ahead of the ACIP recommendation.

So I'd have to, like for example, for Fernando's comment, I had to go back and actually look at the hepatitis A statement extremely carefully to see whether or not family members are referred to. If they are, then we could easily amend the VFC resolution to do it. Otherwise, we'd have to both amend the VFC resolution and issue it as a clarification or addendum to the hepatitis A statement, and then see whether or not that needs to be published in whatever format. With hepatitis B when we basically went ahead, and just notified the states of it and said that, you know, this will be in the hepatitis B statement when it comes out — a misclarification. I mean, they are difficult or if you think of, for example, with the recommended schedule, this year's or potentially for next year's, there might be changes in what the schedule — so if the polio schedule was technically changed a little bit from what was in the polio ACIP statement, which just came out in February. So, you know, I sort of hesitate to get into massive changes of things. I'd really rather just consolidate first and then amend gradually over time. I mean, I do agree that there's some economy of scale just trying to do everything at one time. On the other hand, I don't want to have, you know, a three-day ACIP meeting reading each VFC resolution again and thinking about it.

MODLIN: Comments or questions, issues? Fernando.

GUERRA: I guess the comment would be that we probably need to start keeping track of some of these changes in new recommendations and observations so that we can see whether it might fit in and whether or not they coincide with the opportunities that VFC has provided which, I think, has one of the greatest public health benefits in communities. I think as I see in the instances of hepatitis C, in particular, the very significant increase in numbers of cases of hepatitis C just because now we have screening tests available and, you know, having right now the restriction of not being able to use the VFC vaccine in those instances. Unless one is within an intermediate or a high rate community, I think, you know, it goes counter to the public health opportunity.

SNIDER: That's a good point. If I understand correctly then what John would do is go through again and consolidate the previous VFC resolutions if there are issues that he finds or that the Committee identifies that can be put in the resolutions because they're already in the recommendations. Then we could go ahead and do that, but if there are things that are not in the recommendations and would require a change in the recommendations, then those would just be noted during this process, brought to the attention of the Committee, and the Committee could proceed on whatever timetable it wants to for making those changes in the recommendations themselves.

MODLIN: Right, because they're largely administrative issues. Okay. We've actually bought a little bit of time, which is a good thing. I think we're going to need it for the next topic, which was introduced at the last meeting, and that is the development of guidelines for bone marrow transplant patients — immunization guidelines for bone marrow transplant patients. This is the product of a working group that's been composed of not only ACIP members, but representatives from the Academy of Pediatrics, the American College of Physicians and the American Society for Blood and Marrow Transplantation. This is a topic for which we need both the advice and consent of the Committee for some important issues. Those will be introduced by Dr. Sherri Wainwright. Is Sherri — pardon?

KOVACH: They're on the way.

MODLIN: They're on their way, terrific.

SNIDER: They never thought the Committee would be ahead of schedule.

MODLIN: Would be ahead of schedule — a big surprise. While they're coming, as Chair of that working group, let me give you a preamble as to what one of the major considerations may be. The working group met in October and considered the reason for the need to develop guidelines for bone marrow transplantation. It was the recognition that bone marrow

transplant programs or immunizing their patients after transplantation according to virtually no — with virtually no guidance with whatever seemed to be appropriate to the individual members of the program — with the recognition that in many cases, the immunizing agents and the schedules that were being used didn't always make a lot of clinical or, for that matter, public health sense.

Because of that, they said it was a growing recognition for the need for a more careful examination of the data that were available, and to have a careful consideration of why we immunize bone marrow transplant patients and how they should be immunized. This is an effort that has been underway now for a year, a year and a half. The guidelines that this Committee met in early October of 1997, examined, did a very thorough and careful examination of the available literature at the time, discussed each potential immunizing agent, and then came up with what I think is a very workable set of guidelines that Sherri will present.

What we would like for the Committee to do today is to, after listening to Sherri's presentation and also that of Dr. Keith Sullivan, who has joined us from Seattle as a representative of the bone marrow transplantation group, to number one, what we would like to do would be to get some sort of general endorsement as to whether or not these guidelines are appropriate, whether or not there are important changes that should be made; and number two, some advice as to where to go from here. The thinking of the working group is that it would be nice if this were a set of guidelines that could be — might be a, guidelines that could be issued, not only by ACIP, but also by the other organizations with important input, including the Academy of Pediatrics, and possibly the American College of Physicians and the American Society for Blood and Marrow Transplantation.

In order to have a final document that could be signed off on by all of those organizations, would obviously take a considerable period of time. As Clare and Sherri will present, there is some interest in having a set of guidelines that might be published on a more timely basis, perhaps in MMWR, but the question would be under what egis and under — just what the nature of that recommendation should be. It's probably premature for it to be a full recommendation of the ACIP, but could this be published as a provisional statement from a work group or just what? I would like for the Committee to think about this issue as we present the guidelines. Clare is here. Did Sherri make it yet? Do you want to introduce the topic, Clare, or shall we. . .

DYKEWICZ: Dr. Sullivan and Dr. Wainwright thought that we were scheduled for 2:45.

MODLIN: That's correct.

DYKEWICZ: So they're preparing, I guess. Dr. Sullivan took an 11:30 flight last night, and flew all night and traveled all night to be here. So we really do want to hear him. He's a very senior transplanter from the Fred Hutchinson Cancer Research Center and has been very instrumental in facilitating development of an immunization schedule for bone marrow transplant recipients. We're very pleased to have him here today. If we could just have a few minutes grace, I really think we should try to find him and listen to him.

MODLIN: Okay. Fernando?

GUERRA: I was just going to say that, you know, to occupy a little bit of that time, I just had one additional report from the flu working group that I could bring up now. I was going to save it for after the break.

MODLIN: Well, why — we'll start the bone marrow transplant portion right at 2:45 on the dot, and we've got a little bit of additional business that we can take care of here. We can always take a break if we have to.

GUERRA: I can do it right from here. It's very brief. As the Committee may remember, Nancy Cox had posed those two questions for us to consider regarding the possibility for the development of a candidate vaccine that could move expeditiously into some pilot type of studies. So the working group over lunch recommends that given the urgency of the circumstances, the observations that the federal agencies together with industry, should certain certainly move to develop a pilot or candidate vaccine for use, hopefully before the next flu season. I would so move that as a recommendation for this Committee to consider.

MODLIN: Did everyone hear the resolution? Is there any discussion?

SNIDER: You made a motion? Did you make a motion?

MODLIN: A motion for the Committee to basically consider the resolution. Mimi, yeah.

GLODE: I guess maybe I'd just ask you to repeat it. I just wondered if it had something in it about pilot vaccine and clinical trials or something like that for safety and immunogenicity.

GUERRA: Right. Yeah. I think eventually put — I think the immediate part of this is to develop the candidate vaccine for the pilot trials, the animal trials and moving on to the different procedures. Obviously, the federal agencies involved would work out all of those specific details. Also, some discussion was related that obviously, this could not interfere with the present production of the trivalent vaccine that is needed for just the ongoing influenza vaccination efforts. The idea that maybe trials could

begin by some time in the fall, and recognizing that this is really a recommendation in response to a very specific set of circumstances given the experience in Hong Kong.

MODLIN: Okay. Fernando, would you — Mimi had asked if you would repeat it, just repeat the resolution and then we'll have a bit of discussion about it.

GUERRA: The resolution being that over the next few months, the federal agencies, together with the industry, would develop the appropriate recommendations and steps to move forward with a pilot vaccine or a candidate vaccine for pilot trials over the — probably in the late summer to early fall.

MODLIN: Stan?

PLOTKIN: I was just going to comment that I think Mimi's point is very important; that in addition to the manufacturer, that the federal agencies, and of course, and particularly the FDA, answer the second question that was posed by Nancy — that is the type of clinical trials necessary. Because at this point, let's say a normal flu vaccine does not undergo extensive clinical trials. So that if we're talking about a new vaccine, you want to do these trials before there is an urgent need. So that the time between the order to go, and manufacture a vaccine for mass use and the actual licensing is shortened because you have the clinical data beforehand. So really, you need to look at that aspect, as well as simply the manufacturer of the vaccine.

SNIDER: But it sounds as if the recommendation you put forward addresses the first issue that Dr. Cox put before us.

GUERRA: The development of the candidate vaccine.

SNIDER: So the question is do you also have a recommendation with regard to the second. . .

GUERRA: Yeah. I think the second recommendation would be that then, you know, the appropriate steps to be taken for moving on to clinical trials.

SNIDER: So these could — I mean, these could be done sequentially instead of together. We could address this first issue. . .

GUERRA: Nancy, do you want to comment?

SNIDER: . . .about the recommendations on the candidate vaccine and then have a second motion with regard to the second issue.

COX: Right. I think we got some feedback from the Committee this morning indicating that you would very much like to see children included in the trials that occurred with the H5 vaccine. Certainly, I think that the trials that were mentioned this morning by our NIH colleagues with the subunit or recombinant DNA H5 vaccine will provide the fundamental structure for the nature and scope of the clinical trials that would be done with the inactivated H5 vaccine.

MODLIN: Further comment, discussion? We have a motion on the floor from the Influenza Working Group that we adopt the resolution that Dr. Guerra has now read twice, and has been slightly amended to include encouraging early trials in all age groups with the vaccine. Those in favor? Those opposed? It looks unanimous to me. I beg your pardon; one abstention, Dr. Fleming. Dr. Sherrod, can you hear me? I guess not.

SNIDER: Well, I think the second issue might be worthy of some more discussion, especially in light of Stan's comment. Having been at the VRBPAC meeting and participated in those discussions, since we have a few minutes, I don't think we had an opportunity to — especially to talk in as much detail about the second issue. It seems to me that the programs here at CDC and FDA, you know, might benefit from additional thoughts about these clinical trials. Again, you know, if you're moving into a situation where you're anticipating the potential for a pandemic, and you've got a completely different antigen than you've been using before, et cetera, you know, what are people's thoughts about what will be a reasonable approach to doing clinical trials in these kinds of circumstances because you're caught between two different demands: one, you know, you want to know as much as you possibly can, but then you might need to know it very quickly. So how would. . .

MODLIN: Obviously, one cannot be an efficacy problem under the circumstances. So you are limited to doing immunogenicity trials and you want to get that information in all of the risk groups, which for this virus is virtually everyone. So I think you pick your groups carefully and pick the proper numbers that you need to have some confidence in what your confidence intervals will be around a point estimate for immunogenicity. Obviously, you're concerned about safety, which you'll be gathering that information, but I would think that the numbers of subjects needed in each of the risk groups would be relatively small. Neal, you had your hand up.

HALSEY: Just to be consistent with what I was trying to say earlier — I think having been involved in phase one and phase two testing of vaccines for many years, things go very slowly at the beginning. FDA controls these very tightly, appropriately for most vaccines, where there isn't this great sense of urgency. I think the only thing this Committee could do would be to make a recommendation to the task force that's been looking at this. They may already have this in the statement, but I don't remember seeing

it, but the need to accelerate the trials so that things are done more in parallel than sequential. The concept is there, but this Committee endorsing that would, I think, help the process along because FDA is guided by very strict laws at times in terms of what they can do. So an examination of what would be done in order to be looking at multiple, different products doing dosing studies at the same time as you're doing the safety studies, and so that you don't have to spend three months after doing the phase one studies with one formulation before you can go up in the dose or go down in the age and so forth. A lot of this can be done in a very accelerated fashion; would have to be done in order to meet any targets.

MODLIN: That's an excellent point. It seems almost common sense to me given the potential urgency of having a vaccine available for this virus.

SNIDER: No, but I think, you know, it helps FDA to have the, you know, those kinds of comments.

MODLIN: Right.

SNIDER: I was particularly concerned about the sequencing on these things because I think it is tremendously important to try to move through the process as rapidly as possible. Even though there are some constraints, as we know, there may be some options, some flexibility in terms of how one could sequence and schedule these trials.

MODLIN: Carolyn, did you get any follow-up? Okay. You heard, okay. Fair enough. Any other discussion? If not, yes.

GUERRA: The working group will meet in probably early to mid-May.

MODLIN: Right.

GUERRA: We'll have a follow-up on the status of this. Then the hope is to bring some updated information to the ACIP meeting in June where all of this stands.

MODLIN: Okay. Sherri, you're up. Sherrilyn Wainwright.

WAINWRIGHT: Can you hear me? Is the mike working appropriately? Okay. Good afternoon. As stated in the agenda that you have, we will present a proposed immunization schedule for bone marrow transplant recipients for your review and discussion. Before we go any farther, I would like to bring us up to the same page regarding terminology. Hematopoietic stem cells, as many of you know, our cells, capable of generating white blood cells, red blood cells and platelets, including progenitor cells that are committed to develop into a particular cellular lineage. They presently

can be collected from peripheral blood, placental/umbilical cord blood and bone marrow to encompass all sources of stem cells for transplantation. The current preferred terminology is hematopoietic cell transplantation. This is the terminology I would like to use through the rest of the presentation today. Okay.

At the October 22nd ACIP meeting, the ACIP decided to support the development of a hematopoietic cell transplantation or HCT Immunization Schedule. That was formerly referred to as the BMT Immunization Schedule. In conjunction with the American Association for Pediatrics, the BMT Immunization Working Group and many CDC staff from NCID — the National Center for Infectious Diseases — and the National Immunization Program.

The HCT population is currently not specifically addressed in ACIP recommendations. This process has resulted in a proposed HCT Immunization Schedule, which I will present for your review and discussion, following an overview of background and need in the HCT population that will be presented by Dr. Keith Sullivan. Dr. Sullivan is the head of the Long Term Care Center at the Fred Hutchinson Cancer Research Center. He's the immediate past President of the American Society for Blood and Marrow Hematopoietic Cell Transplantation, and he is the Chair of our BMT Immunization Working Group.

SULLIVAN: Thanks, Sherri. To give an overview, the working group — this has been about a year in genesis and it's been my pleasure to have been tapped by Dr. Dykewicz and the members here at CDC to form a working group. This consisted of Al Donnenberg, who was at Hopkins and now at the University of Pennsylvania, an immunologist; and Donna Ambrosino at Dana Farber Cancer Institute and Harvard, a vaccination and transplant expert to review the literature and to help bring forward some evidence-based guidelines for vaccines and stem cell transplant recipients. So we met and our first meeting was in this room in March 1997. It was important that we had broad input from the infectious disease community, as well as the marrow transplant community from across the country.

Second to that then, guidelines were — evidence-based guidelines were developed, reviewed, modified and presented, as Sherri indicated, in the October meeting in 1997 here at ACIP with Dr. Modlin, as well as Dr. Halsey here in the audience, AAP, Dr. Giller from the AAP and Dr. Abramson, Pierce Gardner and Norm Baylor from FDA. I think that there has been continued — I've been delighted with this progress — has been continued wide input from a variety of vaccine and infectious disease experts. I really want to say that on behalf of the marrow transplant, stem cell transplant community, we really appreciate the efforts of Dr. Dykewicz, and Modlin and others for bringing and drawing attention and drawing expertise to this issue because quite frankly ladies and

gentlemen, there is inconstancy and under-utilization of vaccines and immunization in hematopoietic stem cell transplant recipients.

To get to that point of that firm statement, I'd like to give a little bit of a background for you of some of the biology of transplantation and why I think that this is something that you all need to be interested in. This missile launch, if you will, really represents the current practice of stem cell transplantation worldwide. Last year, there were about 15,000 transplants in the United States. There were about 15,000 transplants in Europe. If you notice the slope of that autologous curve, that is continuing because the technology exists to have GCSF mobilized peripheral blood stem cells collected, and in fact, this is becoming a community standard that practitioners — no longer in research centers or university settings — are providing.

Similarly, the allogeneic curve — brother/sister transplant or unrelated transplants — is increasing for another very good reason. Even though you and I may have a one in three chance of having a matched sibling in our family for a bone marrow donor, for the two-thirds that do not and if you're of common European ancestry, you now have a 70 percent chance of finding an HLA class 1, class 2 matched unrelated donor based on four million individuals worldwide who are in unrelated marrow donor programs and all the HLA types. Thirdly, the slope of those curves is influenced by the fact that the results of transplantation in the early phases are improving. There are more long-term survivors. There's better quality of life and so new disease entities are being applied: sickle cell disease, hemoglobinopathies, auto-immune disease. This is in its infancy, but it's evolving.

So we really need to focus on issues of delayed effects of transplantation and prevention of vaccine preventable diseases. As you can see then, blood and marrow transplant is a hard term to kind of encompass. So HCT for hematopoietic stem cell transplant has been the current moniker. The technique of marrow grafting or stem cell transplantation includes myloablative conditioning. This is either high dose chemotherapy or chemoradiotherapy to essentially ablate marrow function, as well as immunologic functions so the graft will be accepted. Now for an autologous transplant — self into self — there is an obligate period of time wherein the immune repertoire is severely suppressed. It takes on average about six months for immune recovery even after an auto transplant. For an allogeneic transplant, that usually is in the order of six to nine months. I do want to stress that there's a difference in marrow grafting than solid organ transplants. Solid organ transplant recipients are on these drugs of immunosuppression for life to prevent host-versus-graft disease.

The vast majority of allogeneic marrow transplant patients are off drugs such as cyclosporine at around a 180-day post-transplant. Even if individuals develop chronic GVHD, ongoing GVHD issues, their duration of treatment is one to two years post-transplant. That's the reason in these guidelines you will see the potential for a live virus vaccination offered to individuals who are two or more years out after transplant, who are free of graft-versus-host disease and have normal immune repertoire. It also points to the fact that we have to pay attention to when the immunizations would be given because clearly in the first several months post-transplant, one would not muster an adequate immune response.

So the issues are that we need national immunization standards in this unique setting. Clearly, this is demonstrated in the reference list in your hand-out that when surveys have been done, there is woeful disagreement and under-utilization of immunization simply because we don't know who, what, when, where, why and how. Alright. With that as a background, I can vouch for that from our own center's experience. We follow over 3,000 patients currently alive, anywhere from 1 to 28 years post-transplant. In the early years, and we still do have patients come back at the one- and two-year anniversary of transplant. We would write detailed recommendations for immunizations. I can tell you for sure adult oncologists don't have a clue when you ask them to do these things. Patients come back at the second year and they're still not vaccinated.

So finally, we said, "Phooey, we'll set up our own vaccination clinic for about ten years ago. What we need is a schedule that is reproducible, doable and practical." I think that the members of this working group with ACIP input have really done a great job in setting that forward. Also, we need protection from vaccine preventable diseases. The literature is replete with examples of even autologous transplant recipients having no essential levels of measles, mumps, tetanus, rubella at two years, and especially at four years post-transplant. So we do need to pay attention to these diseases, and especially if we have our thesis, and our challenge of this subcommittee and this ACIP consideration, is that we would devise a schedule and plan that would afford protection that would be standard of care for our normal citizens, and especially that would address those vaccine preventable diseases that marrow graft — stem cell transplant recipients are at a special risk.

So how do we approach this challenge? The plan is, I think, that the marrow transplant community stands solidly behind you. We need input from ACIP, CDC, AAP, and we will rally behind it. I can tell you that I've already presented this to ASBMT, our transplant group; to FACT, which is the Foundation for Accreditation of Hematopoietic Stem Cell Therapy. If we have these espoused guidelines, if they get published then, we will stand behind them and those will be part of our criteria for an accredited transplant center. Already, we have 120 transplant centers in the United

States who are on the waiting queue for accreditation. We've done about twenty already. I can tell you that we did this similar project for safeguards of high dose chemotherapy over the last year. We did surveys; we found out what the safeguards were; we set standards out and they got published this month. They are now part of our Foundation criteria. So I think, Dr. Modlin, we really hope from the transplant community's point of view that ACIP can continue to show support for these preliminary recommendations so that we can, in fact, then widen and ensure prevention of vaccine preventable morbidity and mortality from disease.

MODLIN: Are there specific questions for Dr. Sullivan regarding background information or data? Sherri? Thank you, Keith.

WAINWRIGHT: I think this is a real exciting opportunity. It's been great working in this area with Dr. Sullivan, and the ACIP, and NIP and NCID colleagues. What I want to bring you up in your thought process as you're looking at the tables are the general principles for the proposed HCT recommendations that we were considering as we were developing the tables. That includes a rationale for initiating immunizations at twelve months post-HCT as Dr. Sullivan mentioned. It was evidence-based in the literature that was available and most HCT recipients will not respond to most of the vaccines until twelve months post-HCT; and second, the philosophical discussion regarding prioritization post-HCT immunizations.

The first consideration we wanted to give is in recommending vaccinations for vaccine preventable diseases that would we knew were causing — that the HCT recipients were at higher risk for morbidity and mortality early post-HCT, such as influenza, pneumococcal and Hib infections. The second consideration was to recommend vaccinations to catch them up to the general recommendations we have for the U.S. population. Here's a schedule overview. Essentially, the most — I don't know if you can see that — most of the inactivated vaccine series, as stated before, will not begin until twelve months post-HCT. For a series of three doses to — for the following vaccines listed, the recommendation was for 12, 14 and 24 months post-HCT. As Dr. Sullivan mentioned, the recipients were coming back for their check-ups at 12 and 24 months. The 14 months were able to be put in there because that would be supported at the 12 months post-BMT visit.

Studies have been done also to show that levels for these vaccines — one of them in particular, tetanus — the response of the recipient of the vaccine is higher and lasting at that second, at the 14-month visit. So they have first vaccination at 12 months, the second at 14 and that boost last. What they're boosted to last, that immunity is longer than what we would see in a naive — completely naive individual who only had the two vaccinations. The several reasons which would be discussed at length at

a later time would be that there's some donor immunity that could come to the recipient, as well as if the recipient was vaccinated prior to the transplantation, there may be some boosting effect from and any carryover immunity that was there. There are studies that have shown the success of this schedule. It does still need more study. If we have a schedule set, we can look at what it — we'll have bigger numbers to see what's going on with this particular schedule.

A series of two doses of the pneumococcal vaccine at 12 and 24 months post-HCT — we know that very few actually do respond at 12 months, but some do and that pneumococcal is a devastating disease for this group, so that it can provide some protection at that point and then again at 24 months. Then beginning the hepatitis B series and hepatitis A series as indicated with the same caveats as in the ACIP recommendations for those vaccinations. Meningococcal is only recommended to be considered in outbreaks. There's no data at all on HCT recipients. For most live vaccines, such as MMR, the series should not begin until the patient is presumed immunocompetent. As Dr. Sullivan mentioned, presumed competent for this group of individuals is that the patient is at least 24 months post-HCT, is no longer on immunosuppressive therapy and has no graft-versus-host disease. Okay.

I will present to you the evidence-based rating system. You've seen this before. The hand-out is available. It's been used for the HIV/OI Guidelines, and essentially you can follow along looking at the — we wanted to have evidence-based rating for what information was available, and so we know where we need to focus our studies and to improve our — update our knowledge with information. So follow along with your particular hand-out on this as I show you the tables.

Okay. Let's see how I can fit this on here. We'll start over here. Okay. This is the proposed schedule for routine vaccination for the HCT recipients. Again — and a lot of this I have mentioned with the overview so we can go through this quickly — as you see, we split the ages for the DTaP essentially for the less than seven years, and TD for the seven years and older with the series inactive polio vaccine — the series there — and essentially to catch them up to the general population immunity; measles, mumps, rubella with the caveat I mentioned; Hib, hepatitis B, pneumococcal. You'll see influenza here.

We recommended — there's really high morbidity/mortality data high risk for this group, so life-long, seasonal administration; meningococcal as I had mentioned as indicated. Varicella, of course, is contraindicated now, but there is potential for consideration with further study following development of immunocompetency. Then rabies vaccine is not routinely recommended, but it would be in case of — just if it indicated. As you see in the rating, the different ranges of ratings that we're at, so there's still a

lot of studies that need to be done. If you have any questions either now or at the end, they'll be welcomed. I'll either be able to answer them or redirect them to others. Yes?

MODLIN: Mimi, go ahead.

GLODE: I was just going to ask you the experience with the safety of the live viral vaccines because I wondered if it wouldn't be — if safety was a major concern either because of lack of data or data suggesting that, you know, adverse reactions were potentially very serious in that group if given inadvertently too soon or something. If that top half of your table said, you know, "killed, inactivated or purified subunit vaccines" and listed all those, and then right below that, looking almost the same said, "live viral vaccines," and then, you know, had an explanatory caution so you wouldn't accidentally. . .

WAINWRIGHT: That's a very good suggestion. In fact, Dr. Sullivan also in the group had wanted to emphasize which ones are live and which ones are inactivated. By separating them out, in fact, would be a good idea.

MODLIN: That's a good point. Actually, an earlier iteration of this table did have them separated out at one point, but that's a good point.

GLODE: One of my favorite questions to pediatric residents — "Which are live and which are dead?"

MODLIN: Let's go around this way. Dave?

FLEMING: A question about whether you had intended to say anything about minimum intervals or missed opportunities, particularly for the non-live vaccines. If a patient had been seen at 12 and 14 months, and received the schedule as recommended and now comes in at 20 months, do the recommendations say that you should defer any of those vaccines until 24 or that you should go ahead and give them at 20? What do practitioners do?

WAINWRIGHT: That is a good question. Dr. Sullivan, as far as the routine visits. . .

SULLIVAN: Well, I think it depends on the schedule that the patient is. . .

MODLIN: Keith, would you use a microphone? Thanks.

SULLIVAN: Well, the important thing is to make sure it gets done. In other words, if we're four months off one way or the other, I think that that's less important. By the second year, patients are being seen, if they're autologous transplants or patients without GVHD, pretty infrequently —

say, at the one-year intervals. So we would recommend that patients, when they're seen around the 24th month, would be vaccinated.

MODLIN: That's the point. It turns out there is — it was interesting to me to learn that there is a routine post-transplantation visit schedule, much in the way that there is a routine immunization or visit schedule in infancy. It's for the opportunities to immunize that will rest largely with the bone marrow transplantation program. Since these patients are being seen at yearly intervals, then we wanted to take advantage of this. Dave's point is a good one though. If there are opportunities to accelerate — particularly the third dose of vaccines — if there is an opportunity to do so, it may be that we may want to be permissive in that respect in terms of allowing the third dose to be given earlier than 24 months of age. I'd be interested to know how others feel about that. It makes sense. I think we can add some language to that effect. Rich.

CLOVER: You made one brief statement regarding this, but didn't talk about it in detail. One of the recommendations, if any — and I assume it may be a timing issue — of vaccinating these recipients prior to the transplant to help them in that first year of post-transplantation.

WAINWRIGHT: There have been a lot of — many studies looking at that particular issue. Dr. Sullivan?

SULLIVAN: I mean, it's a beautiful construct, but it doesn't work very often; in other words, the issue of a patient suddenly developing leukemia and endoblast crisis, or suddenly there's an unrelated donor available — that sort of thing. So I think we've tried to do that and it's mostly not been successful for a variety of logistic issues.

MODLIN: Chinh.

LE: I'd like to thank you for a very, very concise document, you know, compared to the other MMWR. Everything is just right; no redundancy table forms are great. I really complement you for that. I remember during the working group, we have a strong emphasis on another topic which is not included in your final version, which is documenting the area of needed research because many of the recommendations, as you can see, are B-2s and B-3s. We're flying by the seat of our pants making recommendations on very little amount of data. The point of the recommendation is to be as a — just a step, a first guideline to do something with the understanding that we need, number one, continued surveillance of the epidemiology of the vaccine preventable diseases, and how much the vaccine use will be done after the issuing of these guidelines, and making a strong statement like "we strongly encourage the centers to enroll patients in clinical vaccine studies." We know how bad the pneumococcal — the present pneumococcal vaccine is and there

should be a strong statement that they should be enrolled as much as possible in conjugate vaccines, for example. It's those areas of needed research that need to follow as part of the document.

SULLIVAN: Well, I couldn't agree with you more. If nothing else, the strong backing of ACIP to come forward with minimalist approaches and we need resources to be able to have national registries, and to be able to do the tracking and monitoring so that we will be able to do an experiment; see what happens and where are we two or three years to present to this group again.

WAINWRIGHT: It could be included in the text.

MODLIN: Clare, did you have a comment?

DYKEWICZ: I just want to — I understand your point. I think that's a very good point, but in the interest of time today, we were just going to discuss the schedule itself. Hopefully, after we get through this, then we can discuss additional issues.

LE: So this is not the final document?

DYKEWICZ: What is being shown to you today is not the final, explanatory joint statement explanation, which hopefully will be published, explaining to everybody why they should do this. So right now, we're just discussing the tables.

MODLIN: Bill?

SHAFFNER: First, my compliments to the chefs. I think that this has been a wonderful process in the way it's been developed. Now that we're up to this, let me ask a few kind of word smithing questions. I note, for example, in table one that this is the proposed schedule for routine vaccination, et cetera. Well, there's some interesting vaccines included under this rubric of routines, such as rabies or I might even ask hepatitis A. Yet others, typhoid vaccine off the top of my head, have not been included. So perhaps we need a change in title and either be a little bit more exclusive or a little bit more inclusive.

WAINWRIGHT: I understand your question. It's a very good question. I have other tables also for travels and for health care workers, which include the other ones you had mentioned. As far as hepatitis A, and it does say "routine administrations not indicated," we wanted to include it. There were certainly reasons that we wanted to address these particular disease in this table. The actual, I guess, pointing out of the change in language, we could alter that. There's not a problem there.

SHAFFNER: They would be for your consideration.

MODLIN: Maybe I could address that just very, very quickly. Fortunately — very fortunately because of the good work of Keith Sullivan and his colleagues — many of these patients return to normal or near normal existences in which they travel. They get exposed to bats. They run into all of the problems that the rest of us do, and so inevitably questions will come up regarding both the safety and the efficacy of immunization with all — virtually all vaccines that we have available. So we actually sort of extended our original purview to think about some of these additional possibilities because they will inevitably come up. I think your point is very well taken about the word "routine" and I think we may drop some from this first list and put them in other places. We might have one on — a category of special situations, special considerations that would be appropriate.

SHAFFNER: Right.

MODLIN: Again, I think we can do some, a little more, a lot of cleaning up here and some more — of course, we're thinking about that, but yeah.

SHAFFNER: I have a couple of just other quickies.

MODLIN: Sure.

SHAFFNER: One is I might suggest that you in some way order, particularly the routine one, in order of importance just as you have discussed — just as you've made the presentation today. Some of us might put inactivated polio vaccine down a little bit lower and put pneumococcal, for example, a little bit higher. Then the third thing is — and I think I just missed this so I'm asking for information — you treat measles, mumps and rubella vaccine in one way, but varicella vaccine in a very careful and different way. Did I miss why there's a distinction?

WAINWRIGHT: I'll definitely — the actual studies have been done.

SULLIVAN: We have data on the MMR from Herr Lugan at Caralinska. They're pretty good data and most of them been accepted in the United States, no data on the second.

MODLIN: In addition, Bill, we have a varicella statement that says, "the vaccine should not be given to immunocompromised patients" so that we really — to say anything here would be directly to contradict the current varicella statement; whereas, with measles vaccine, it's a little bit different in that we have some data. It looks like it is safe to be given at 24 months of age and so that's basically the reason. Stan.

PLOTKIN: We have to be careful about our words because I thought we were talking about people being reconstituted and immunocompetent at a certain point.

MODLIN: Yes.

PLOTKIN: I had remembered that point and so I think we have to be a little careful.

MODLIN: Well, again as you see, the fine print with varicella includes a call for studies in this group under appropriate circumstances.

PLOTKIN: Well, I had two questions and one of them directly relates to Bill's point. Varicella, as you know, has been tested extensively in immunocompromised patients. I couldn't see from where I'm sitting the wording on your varicella, but I wonder if you are precluding studies by saying that it's not indicated. There — again, as you know — there are criteria for the use of varicella vaccine in immunocompromised patients. I guess I'm surprised that they haven't been applied here.

MODLIN: Stan, these were extensively discussed. I think the point was that we had some data with measles, but not with varicella. There certainly was a consideration that if there — varicella vaccine could be used safely in this group that it would be a highly desirable thing to do. We actually say "the use of varicella vaccine should currently be restricted to research protocols for recipients."

PLOTKIN: I see.

MODLIN: So I think the idea would be to encourage studies under appropriate protocols.

PLOTKIN: My second question is — was any thought given to laboratory determinations of immune response in this population which isn't that large using indicator antibody tests to determine whether people have responded?

DYKEWICZ: I understand your concerns. I thank you for your comments. I think the point to remember regarding the data on varicella vaccine use in immunocompromised populations is that most of the data come from studies in leukemic children who are in remission, who are on maintenance chemo, which is a very different population than a person who has just undergone an HCT transplant. Those individuals in the latter group are much, much more profoundly immunocompromised with B&T cell deficiencies. We don't have any data on the varicella vaccine use in this particular population.

We did have a conference call a couple of months ago with Ann Arvin and Ann Gershon, as well as Raleigh Bowden from Fred Hutchinson and NIP to discuss what our recommendations should be regarding varicella vaccine in BMT patients. Basically, they said there are no data. Ann Arvin is very concerned. She said, "We know that even though it's an attenuated strain of vaccine, we do not have any evidence that its T cell virulence or whatever is attenuated in any way. We don't know that the T cell response to the vaccine strain virus needs to be any less robust than in an exposure to a wild type vaccine." So the advice that we were getting from people who have done these studies, who have a lot of experience in using these vaccines and leukemics is we have no data in BMT patients and we don't know. Until we have further data that has been collected in a carefully accessed manner, let's just say we don't have data and go from there.

MODLIN: Clare, did you want to address the issue of post-vaccination serologic testing? Keith?

SULLIVAN: That's a great question. Boy, did we grapple with that one. I'm sure there's not a real answer right now because there are three variables or co-variants. One is what is the transplant? In other words, is an autologous the same if it's CD-34 selected? Is an allogeneic the same if it's T cell depleted? What about if you're a mismatch or an unrelated? So there are different types of stem cell products. There are different types of underlying disease. Is a chronic phase CML patient intrinsically different in the immune repertoire and recovery than a non-Hodgkin's lymphoma in the fifth relapse?

Third, is the published literature on the issue of titers that kind of are the end result of those two first variables often have different technologies or different techniques for read-outs, often different end points of the read-outs in the literature? When we actually tried to do this in the field with physicians getting levels done in their local institutions or their state, then this is really, I mean, a lot of flutter was going on. I mean, it was how do I do it? Where do I send it — that sort of thing. So I think unless we have the resources, perhaps clinically-based research in this area so that we can standardize these sort of things, I think that there's just too much heterogeneity there to really rely on.

MODLIN: Yes, the lady back — could you introduce yourself please?

McHUGH: Well, this — I'm Yvonne McHugh, Chiron Vaccines. This goes back about five minutes in the discussion; we were talking about routine designation for rabies. I know that we usually think about rabies vaccine for post-exposure prophylaxis or for travel, but it is a routine immunization pre-exposure for a number of occupations.

MODLIN: Thank you. Neal?

HALSEY: I think we were — I was going to add to the serologic testing issue. I think we decided that we didn't want to make any recommendation about doing it now for the reasons that Keith talked about it, and that it's not practical, but we did make a recommendation that once these guidelines are out there and published, that there should be a very careful study, perhaps a multi-center study to collect serologic data to look at the response rates, and also a question with regard to persistence of antibody over time. So we did make a specific recommendation for a study to be done to evaluate that.

MODLIN: Fernando.

GUERRA: Two questions: one, Keith, what was the distribution — the age distribution — of the individuals that have received transplants over the last few years? Two, has there been some experience in those individuals that are post-transplant who have been challenged with naturally recurring disease who are post — who have been vaccinated against some of those?

SULLIVAN: The age distribution is in most centers, there are a very few handful of centers in the U.S. that do only pediatric transplants. Most are mixed centers even though they may have two hospital components. You have two different centers, but it's the same transplant team. So there are very few that report only pediatric experience. By and large, the transplanted cohort is about 20 percent or under age 18 in most centers. In the upper age limit, senior citizens used to be defined as 40; now we go up to about 65 as the faculty ages. So I think that we're dealing — most of the bulk of the patients will be adult and not children.

The second question you asked is if someone has been immunized at a schedule somewhat like this and they had been rechallenged. We don't have many examples of failures like that. With the egregious ones, we do have of an individual who didn't get immunized with influenza, who had an unrelated transplant, who died of influenza at eleven months post-transplant — something like that. I mean, I don't have a good handle to really answer your second question as to the clinical efficacy. Our big problems really are dealing first and foremost with the virus. Granted, the vaccines are crummy vaccines and there should be — well, not crummy — but it's not ideal all the way. Well, we can get rid of it, but we also depend on chemoprophylaxis a lot too.

In this setting, there's functional asplenia and there's chronic graft-versus-host disease. There's a whole reason that people — individuals can be heir to encapsulated gram-positive, overwhelming pneumococcal sepsis sort of syndromes and *H. flu*. I think that a lot of this has been to the herd

immunity in the United States. We're seeing a little less *H. flu* right now — thank God — but I mean, these are major tickets. I think that the comment on "why don't you put the important things at the top on table one" is really well taken. I guess influenza really has to be up there also.

MODLIN: Sam.

KATZ: I have a question and a comment. The question, Keith, was you answered previously, I think, in relation to recipients receiving pre-transplant immunization. Are there data on donors. . .

SULLIVAN: Oh yeah.

KATZ: . . .when you have allogeneic rather than autologous?

SULLIVAN: That's a question going both ways. Certainly if you do — the ideal would be to boost the patient and the recipient pre-transplant and that's clear. You have obvious loss post-transplant, but then the twelve-month boost is even better — that sort of thing. It's just really hard to get all those logistics for both donor and the recipient together.

MODLIN: I think the problem, Sam, is that when the working group looked at the information that was available on donor immunization, we didn't feel like there was enough information there to be able, at this point in time, to make a recommendation, but exactly.

KATZ: I guess that goes along with what Neal was suggesting, which I would only second. There are examples. I appreciate your problem with disparate data from different labs, but you can get some funds from NCI, or what have you, and set up one reference lab and let them do all your testing. That's the way the ACTG does many of its HIV studies in pediatric HIV, or else have certified labs that have gone through with standards and shown that they get the same data. So you should be able to acquire those.

SULLIVAN: Well, it would especially help if an August body like this starts making those suggestions also. I mean, and that really would assist.

MODLIN: Carolyn Hardegree? Norman Baylor was part of our working group and obviously reported back to you. I don't see Norman in the audience today, but obviously, there are issues for the FDA. Would you like to comment?

HARDEGREE: Well, these schedules and recommendations for use in bone marrow donors and recipients are obviously not part of the label. I think Norman has indicated, however, that, you know, that he's made the statement. If this group feels that recommendations need to be made, then that, you

know, that needs to be done recognizing that it is not in the label. However, I think the points that are being made about trying to collect data then become very important because you would — if that data existed, then maybe the labeling could include information about the use in these populations.

MODLIN: Good point.

SNIDER: I also need to point out with regard to that issue that CDC and FDA have a committee on collaboration, which I co-chair. We've talked about issues like this, and actually, Stewart Nightingale has provided us with some language to use in our CDC documents. When there is not information in the package insert, we can go ahead — we have an understanding that we can go ahead and publish these recommendations, acknowledging that the information is not in the package insert.

MODLIN: Thank you, Dixie. Further questions? Neal?

HALSEY: John, there are two minor points; that you're asking that this go out to everybody for comments. I detected two errors, I think, in the document in re-reading it just last night. On table one footnotes, footnote E, I believe that the working group determined that we should be following the same table that is used for measles immunization that's in the general recommendations and in the Red Book with regard to the interval from last dose of immune globulin. It's not a fixed eleven months. It's variable based upon the dose of immune globulin that's given. So I think we can correct that one. Then the second is a relatively minor error. The footnotes for table two on C is that it says "there's no evidence that live attenuated vaccine strain viruses and MMR have ever been transmitted from person-to-person." There is an exception to that. Ginny Losonsky at Maryland did a study that demonstrated postpartum women who were breast-feeding. There was rubella vaccine virus transmitted to the infant although it caused no harm. So I think we can just — so everybody doesn't have to make the same corrections, we could just address those two.

MODLIN: That could be slightly modified. Okay.

HALSEY: But there's no household transmission.

MODLIN: Okay. Fernando?

GUERRA: The recommendation is not for, say, the primary care physicians of this population to participate in this kind of a schedule. Is that correct? This is really to be done within a specific center and where they can be monitored closely?

MODLIN: Let's ask Keith to respond to that.

WAINWRIGHT: My understanding is that they would be at these centers during this time.

SULLIVAN: As much as possible, but when we looked at our — we have about 1,800 current, active physicians caring for our patients. About half of them actually are non-specialists. They're internists, generalists or pediatricians. Often in the first year or two, the hematologists working with the transplant center — the oncologists working with transplant center would be the primary transplant type person, but there will be a local community doctor also doing monthly counts or something like that. So I would say that much of this would still be done in the field. We will try to bring the patients back at the second year, but in fact, they may because of limitations from HMOs or something like that, you may have generalists or oncologists/hematologists doing this.

GUERRA: I guess it's not clear in the way that, you know, these are laid out. Certainly, these schedules are really way out of sync with what the primary care physicians are accustomed to. I guess if given such a patient within a primary care system, there would be information going back and forth in terms of these recommendations.

SULLIVAN: Absolutely.

MODLIN: I don't think the intent is to have the recommendations directed necessarily to the bone marrow transplant group or any other group of physicians. It's recommendations for the patients and they will be carried out probably differently at different centers, but what we've heard from Keith in the past is that particularly with bone marrow transplant patients, that referring physicians or other oncologists are reluctant to do anything without the advice and consent of the transplanting physicians, and that for practical purposes, many of these things are carried out at the transplant center. Dr. Gilmet.

GILMET: Do you anticipate requiring any *in vivo* or *in vitro* quantifiable evidence of immunocompetence other than that two-year window you mentioned?

SULLIVAN: Well, there's a variety of tests that have been evolving over the last decade and a half; and no, we don't because there is no one particular assay, whether you use T cell subsets or response to antigen, what-not, and so that is the research part of it if it is not a clinical practice part of it.

MODLIN: For purposes of having a simple statement, we do have immunocompetence defined in the statement, which is specifically an individual who has achieved — survived 24 months post-transplant without graft-versus-host disease, which I think is reasonable for routine

immunization purposes, for these purposes. It's not a very specifically laboratory defined definition, but the working group thought was reasonable for these purposes. Bill, you had another question?

SHAFFNER: Just a quick comment and perhaps a small suggestion. The issue that was just under discussion concerning who is actually going to immunize these patients, I think epitomizes a more generic issue that relates to the care of adults. Care is often fractionated, and as Keith said, oncologists and many other specialists who care for adults are not aware of this Committee, its recommendations and do not conventionally administer vaccines — many of them. So perhaps we might begin now as we're designing this wonderful car, as it were, how to market it. I think we ought to give a little bit of thought about how it is these recommendations actually find their way into the hands of the physicians who are going to be doing the immunizations — starting certainly with Keith's colleagues and how it is all of us can help with that, but then extending it even beyond. Perhaps if we work our way through this, we'll learn something about how it is we can communicate more effectively with a whole array of providers who take care of adults. It's a very different issue than when you're delivering vaccines to children.

SULLIVAN: Okay. Here's a new standard for immunizations and then do some sort of — I mean, there are a lot of new procedures that, you know, have been two years later, how many people are actually doing that and what are their characteristics. Have you all done that for immunizations?

SHAFFNER: Not as effectively as perhaps we ought to, but perhaps this is a way that we can get some of the national, professional and scholarly organizations that have to do with adults a little more energized.

MODLIN: Thanks, Bill. That question actually leads specifically into the next area, which I really would like to get some sense of the Committee as to where to go next. There's no question that the working group felt that it was desirable to ultimately have a statement that could be a joint statement or as close to a joint statement as possible that involved several organizations with interest in bone marrow transplant patients — or immunization of bone marrow transplant patients. That's a goal, however, that inevitably will take some period of time to achieve to have a final written statement that we can endorse. There — a number of us have felt the need to perhaps have this set of guidelines available for dissemination in some form a little bit earlier. The question is just how best to do that and would it be reasonable, as for example, to have this set published perhaps in the MMWR, perhaps another professional publication as it stands now with the concept that this is a — these are provisional recommendations that have been formulated by a working group, and that they are subject to, certainly subject to change over time. They may very well differ, at least slightly, from what ultimately would

appear in a published joint statement — not only from the ACIP, but from other organizations. Neal, do you want to address that issue from the Academy's standpoint?

HALSEY: I think the only circumstance I'm aware of where draft recommendations are published was the *Federal Register* publication of the polio statements, which I don't think we necessarily favor for a routine process. From the standpoint of the Academy, we have — when we started this process, we put in a statement of intent to our Board, which has approved the development of such a statement. So we're on a green light to proceed from the Academy and we had several people participating in this process. I don't see any difficulties. I suspect that there would be very little, if any, changes in the language that would ever be requested from the Academy. So I think we can put it forward for final clearance at this time and any final comments within a reasonable time period. I don't see this one as a problematic one at all.

MODLIN: Okay. Pierce, any comment regarding that issue?

GARDNER: Well, the approval of joint things by the American College of Physicians is more cumbersome. So I would — I don't know what the time frame would be for that, but I think there are other organizations that would go forward with it. I'll try to get it through the ACP.

HALSEY: John, just an idea.

MODLIN: Yeah.

HALSEY: Just an after-thought, and I mean, Keith can answer this. There aren't that many major bone marrow transplants. I think one way to get it out and disseminate is just to copy it to the 20 or 25 — whatever the number is; I can't remember — of bone marrow transplant units. Maybe they are proliferating even faster — 40, 50?

SULLIVAN: One hundred seventy.

HALSEY: But one could disseminate — well, if there's 70, one still could disseminate.

SULLIVAN: No. One hundred seventy centers now that we know about.

HALSEY: That's too many.

SULLIVAN: Yeah. So but I do think that there's a mechanism for getting at that transplant group through the transplant-specific journals.

HALSEY: And you can — well, but I'm not saying you have to publish this. This is still a draft and publishing it there is circumventing the usual process. It's already been disseminated a fair amount amongst the transplant community just in the process that this has undergone. I don't think there's a problem of asking for comments — sending it out, you know, and asking for comments. That's one way to give it to them. They can even start using it if they want to. At the same time, we're going through the clearance process for everything else, and set a deadline of two months for comments and then we move on from there.

SULLIVAN: We have our national ASBMT meeting on the 25th of March. If it would be okay with ACIP, what I had planned on doing — and the AP — is plan on giving this draft to the Board so that they could digest it, sort of thing. Now if you wanted to have wider dissemination, then that can go back to their parent institutions.

MODLIN: Fernando?

GUERRA: To follow up on these recent discussions, it seems to me that this opportunity should really serve to open up the much bigger opportunity. The sentinel condition of the marrow transplant perhaps could allow us to bring this population that is being transplanted, whether with stem cells, marrow transplants or solid organs, or that have some very special circumstances that affect their immune status, that affect their overall physical health and well being that are today in a state of good health. They're living longer. They really, I think, need to be addressed in a way that we lessen the apprehension that primary care physicians have for taking care of them. I think that there have been a lot of missed opportunities for immunizing and protecting them because of this great fear. I think what I hear Keith saying is that, you know, this is a time to really begin to bring them closer to the mainstream in terms of protecting them, I think, as we assemble information. So I certainly support what Bill was suggesting; that somehow we need to be able to communicate this to the broadest possible audience.

MODLIN: Okay. Any further comments? I sense from the Committee that there's no opposition or major opposition to disseminating this information as is with the proviso that it is obviously a work-in-progress, and that recommendations can, and obviously, it certainly will change as new information becomes available. We probably will continue to work within the ACIP towards — with the other organizations towards working towards a joint statement. Keith, Clare, Sherri. . .

SNIDER: Maybe I should say something in terms of CDC expectations. I don't know of any precedent for putting anything in the MMWR in a draft form requesting comments.

MODLIN: Well, this had actually — Clare, you may want to address this — but this actually will be part of guidelines addressing bone marrow transplant patients of which immunization is only part of that, but there's already a working document that's well along.

DYKEWICZ: Right. Well, we had — the original plan was to include an immunization schedule in the BMT guidelines, which will be published by the MMWR later on this year. It's got to go through cross-clearance and that will take a while as you know. I guess our concern was if that doesn't get published until the late summer or the fall, do we want to try to get this immunization schedule out to the public before then?

SNIDER: I don't mean to throw cold water on anything. I just wanted to have a clear understanding with folks that I think it's fine to get input through other mechanisms, but just for clarification, I don't think that we have a precedent for putting things in the MMWR for comment from, you know, back to CDC. So I just want to make sure that we are ruling out the MMWR as a mechanism for getting these out quickly, but I think sending them out through other channels is perfectly fine and probably a very wise idea.

DYKEWICZ: Well, I guess my concern is that I would like to get a schedule out as soon as we can. I think that would be helpful in dealing with the confusion that currently exists. If we delay distributing this to the public until the statement comes out, then that probably will not come out for another year maybe. Then we — are you suggesting then that we not have an immunization schedule in the BMT guidelines and that we delay releasing this to the public until the statement comes out a year from now, which I think may be a bit long?

MODLIN: No. What we had discussed would be the possibility of including this schedule with the BMT guidelines that address a number of issues.

SNIDER: And that was through the regular clearance process of CDC.

MODLIN: Yes. Exactly, but it would contain language suggesting that this is not final recommendations yet.

DYKEWICZ: And then, I guess then the other issue was some have suggested that even waiting that long to get it published in the BMT guidelines is too long and they want to see it out in print somewhere in some fashion so that the centers can get it this spring.

MODLIN: Further comments? Let's take our break. I'm sorry; I beg your pardon, Keith.

SULLIVAN: Neal, you said it was at a green light by AAP. Do you have a time frame on that?

HALSEY: It will take two to three months to get clearance through the Academy if everything goes well. Then publication is another three months, but it's just we do not have any objection to publishing the table as part of the bone marrow transplant guidelines. You just simply can't use AAP endorsement until we go through the whole process. So it's a CDC table then at that point, but there's no objection from our standpoint to you doing that.

MODLIN: Okay. We are actually a little early. Perhaps in the interest of maybe keeping ahead of schedule, let me ask that we come back at 4:00 to begin the discussion on rotavirus vaccine.

We have a quorum; we'd like to go ahead and get started, please. The last item on the agenda is an extraordinarily important one. We'll be revisiting a topic that we have talked about each of the last two meetings, perhaps three, and we believe have some important decisions to make at the meeting today, I hope. Dr. Roger Glass and Joe Bresee will begin the presentation. Roger?

GLASS: Thank you, John. I feel like I'm — can you hear me? Is the microphone on? Yeah, there is it. Can you hear me now? Yes? I feel like I'm here amongst old friends. This is a dialogue that really began 2½ years ago — October 1995 when we had a fifth rotavirus workshop when we had a one-hour symposium on the disease of rotavirus, and the two vaccine candidates that were in the process of development. Every meeting for the last five meetings, I've been up before you to continue this dialogue. You've asked many questions. Is there a need for a rotavirus vaccine? Are the vaccines being developed, particularly the rhesus, safe? Is it effective? Who should it be given to? Who are the high risk groups?

Over the last year and a half or so, since really October of 1996, we've gotten up at each of these meetings and presented the data that we have available. We let you know in those presentations that rotavirus was the most important cause of childhood diarrhea in the United States and in the world. We let you know that 3 or 4 percent of all hospitalizations of children under five were for rotavirus, about 50,000 hospitalizations a year, 20 to 40 deaths, a half a million doctor visits and so forth. We've presented data on the cost effectiveness data presented by Andy Tucker who's with us today. Then we've reviewed the vaccine studies. In October, the last meeting, we had data from three new vaccine studies that were all published in the month of October 1997, a propitious event. All showed the efficacy and safety of the vaccine.

We've talked about the complications — the low and frequent complications — such as intussusception. We had Peggy Rennels present data on those complications. We've discussed the low rates of fever in the vacinees compared to placebo recipients after the first dose, and on the third to fifth day after vaccination. So we've covered over the past year and a half — 2½ years really — many of the issues and background for rotavirus. What's happened then since October, our last meeting, 1997? Nothing's happened; there's no new data. There's nothing new that's happened with one exception. I see Carolyn Hardegree looking at me. In December, the FDA had their — in their advisory committee, reviewed the rotavirus vaccine data. The advisory committee unanimously gave their approval for the licensure of this vaccine.

So that what has really happened is that between now and the time of the next ACIP meeting, we expect or anticipate that the first rotavirus vaccine may be licensed. Yesterday, the Rotavirus Working Group of ACIP chaired by John Modlin here met for the afternoon to go over the recommendations. Now these are recommendations that were distributed to all of you on February a year ago — just a year ago now. They were reviewed and we've took many inputs from many members here and outsiders — participants from the American Academy of Pediatrics and the American Academy of Family Practice.

We've collated and pulled together all of those in subsequent drafts that were distributed to you in June and in October. So you've had three successive drafts to think about, to scratch your heads with. Our committee decided that in view of the fact that we have no new information — we will probably have no new information prior to licensure — and we've aired most of the discussions that we thought we responded to your questions; that it would be important for us to come and have this group come to a decision or recommendation so that when the vaccine would be licensed, we would be in a position to provide guidance to physicians in the United States.

The target here is to try to reduce the tremendous morbidity in the United States from mild and severe rotavirus diarrhea; to try to visualize in a few years a decrease in 3 or 4 percent of hospitalizations in children under five; to try to decrease diarrhea hospitalizations, particularly the hospitalizations in the winter attributable to rotavirus; and to decrease doctor visits for diarrheal disease significantly by 20 to 30 percent. So since this is the last meeting before the FDA decides on licensure, we thought that we would, rather than present any new data, we would just go over the discussions and the deliberations of our Rotavirus Working Group meeting yesterday.

So I'm calling on Joe Bresee, my able colleague, to go over those recommendations one by one. Those of you on the Committee should have your drafts of the recommendations from October. Does anybody that doesn't have their recommendations with them? Andy, could you give those people with their hands up recommendations? They're under my seat. We'll get you recommendations so you can follow through where Joe is going. We're going to — keep your hands up. Andy, just for the people who don't have them on the Committee, please, because we — we went over these recommendations yesterday in detail. Joe will go over the changes to those recommendations that have been made and highlighted. These will be edited and reviewed by our Committee members, and then a final version of the new recommendations will be sent out to ACIP members shortly thereafter. Okay. So without further adieu, let me turn the meeting over to Joe Bresee then. Joe?

BRESEE: What I'd like to do now, I guess, is go through some of the discussions that we had yesterday at the working group meeting, and maybe outline you some of the issues that we discussed and the consensus that we came to. I think miraculously enough maybe, the working group tended to come to general consensus on every issue that was discussed. The first — and what we'll do here is go through each of the kind of major or minor issues that we discussed yesterday. Maybe we won't get to them all, but the first ones are the major ones; go through each of them, talk to you briefly about what the issues are, the way the discussion went and the consensus opinion that we came to, and whether it wasn't a consensus to point that out.

Really, it represents a laundry list of the issues that were raised by ACIP members in reviewing the October draft, or by other interested parties or other people who know a lot about rotavirus. They came up with these great questions that we worked on yesterday. What we'll do first — and before I say that, let me say that the recommendations that you have in your hand are actually new from October. What we did was left the highlight and the strike-out in the document. So what you see there are the changes since the October draft of the document, and represents some of the thinking of the working group from yesterday though it's not yet reviewed by everybody. So we ask you to do that, but I think they reflect accurately what the working group decisions were yesterday as will these slides.

The first thing that we spent, really the lion's share of the time on yesterday and likely will today again — and what I'll do is I'll go through each of these issues and maybe pause after that to allow for some discussion of each issue as they come up. I think we spent the lion's share yesterday on recommendation one in the October draft, which is still recommendation one in this draft. That is, who are you going to vaccinate and how strongly are you going to recommend vaccination in

these groups? The October recommendation says this. It says "the ACIP recommends universal immunization for all term infants greater than 37 weeks of age with three oral doses of rotavirus vaccine at 2, 4 and 6 months." Ignoring now for a minute — I'll draw on this as we talk — ignoring now the references to whether you're term or not, we'll get to the rest.

The options were really — were three; maybe there were four options that we could address. Do you vaccinate everybody as routine immunizations with other childhood vaccines? Do you give a permissive recommendation where you say people can, or may or should be vaccinated? Do you vaccinate a selective portion of people or do you recommend a variety, a combination of these approaches where some populations of children are recommended with different strengths than other children — other populations of children? So the first thing the working group spent a lot of time on yesterday is trying to identify subgroups of kids, or small groups of kids or high risk groups of kids that would be at high risk for severe disease, which would be the target vaccination. I think — my notes — I think that after a lot of discussion, we first listed all the groups that we could possibly include in this selective vaccination program — things like premature babies, kids with immunocompromising conditions, kids with a low socioeconomic status, kids in daycare. In the end, I think we decided that because rotavirus — as Roger is prone to say — rotavirus is a "democratic" disease. It affects every kid in the United States.

Because high risk groups are difficult to identify — particularly at two months of age — by the time of vaccination, they may change. Because there's very little data on the risk of rotavirus by these high risk groups and because of the severity of disease, it probably related to so many different factors, and again, very hard to predict by the time of the initial vaccination. We decided that recommending a vaccination program targeted at certain high risk groups is probably not the wise thing to do. So we were left then with the top four. So we disposed of E first maybe and were left with the top four, really divided into two groups: vaccinate everybody or maybe a permissive vaccination recommendation. Again, we quickly decided to throw out A maybe because we didn't like the word "strongly" and it wasn't used for other routine child immunization, and may ought to be reserved for special situations.

We finally decided, and I think we came to some consensus about this or general consensus in the group, is that kids who — we wanted to send a clear message to pediatricians and health care providers. We thought that if we made a recommendation that rotavirus immunization should be considered or maybe considered, that uptake of the vaccine would be poor and that the goal of vaccination — that is prevention of severe disease — would be undermined. Because we feel a rotavirus disease in

the United States — the burden is so high; the vaccine works very well; the safety of the vaccine is fairly well established — that recommendation for all kids to be vaccinated would be the most appropriate recommendation. So the recommendation the way it stands is this; the way it stands in the new draft is this, is that "the ACIP recommends routine immunization for all infants with three doses of rotavirus vaccine at 2, 4 and 6 months of age."

The reasons again for this are that the large burden of disease among U.S. infants with near universal infection rates; inability to identify or target groups of high risk for severe disease; adequate data regarding the efficacy and the safety of the vaccine; and that the vaccine program is likely to yield a cost savings; and finally, that we wanted to send a clear message to pediatricians so there wouldn't be any ambivalence about the recommendations. Maybe I'll stop there after that one and open it up for discussion. If any of the working group wants to elaborate or correct what I've said, feel free to chime in. John?

MODLIN: I wonder if it wouldn't be wise to go to the next couple of points that were discussed by the working group, Joe, because they really do, in some respects, they're independent of the routine recommendation, but they are — inevitably, the discussion regarding routine immunization will raise these other issues. So I think discussing the age and the precautions will probably be important. So I would suggest going through those first two or three.

BRESEE: The second major issue that we discussed yesterday — and again, took most of the rest of the time actually — it was the age of immunization. The problem was there were dual concerns of vaccinating enough children, so for including enough children in the vaccination program to adequately decrease the burden of disease, but there were some data and some concern that initiation of vaccination in kids older than six months would cause increased adverse reactions. So there was a balance between how old — how much adverse reactions were you willing to tolerate for a decrease in burden of disease. The way the October recommendation read is this — is that "children older than 24 months of age are likely to be immune from natural infection, and therefore, initiation of vaccination with RRR-TV is not necessary for these children."

The alternatives, again raised by the ACIP member from the last draft, were that we could recommend vaccination for kids under six months of age or thirty weeks of age; that we could — and this is the age for which all the vaccine trials have been conducted — that we could we could vaccination for only kids under a year of age or for only kids under three years of age. The relative benefits of these were that in the kids less than thirty weeks or six months of age, again, there's data for these kids. All the vaccine trials, all the efficacy trials have included the vaccination of

kids — initiation of vaccination of kids up to six months of age or up to thirty weeks of age. So there's clear efficacy and safety data for these kids.

The benefit of the later age group would be that we know that about 25 percent of hospitalizations or severe disease occur in kids between two and three years of age. So limiting the — and so extending the vaccination age group up to three years of age may be able, may allow you to prevent these illnesses. The committee was, I think, presented some data by Dr. Peggy Rennels yesterday that I think was compelling in showing that kids who received their first vaccine that are older than five months of age really do have — may have higher rates of fever, which may become a problematic public health issue, as well as an individual issue. I think because of that and because the fact that all the data collected so far on this vaccine is really limited to the young kids less than six weeks of age and limited to vaccination of kids — the complete series of kids under a year of age — that we decided to limit our recommendations and change our recommendations for the age group.

So the recommendations now read "vaccination may be initiated at any time between six weeks and six months of age with second and third doses following the preceding dose by a minimum of three weeks;" and second, that "all doses of vaccine should be administered during the first year of life." Again, this is an agreement with all the studies and all the data that have been collected and may be relatively conservative. Hopefully, with post-licensure studies if it's proven that vaccination of older kids is safe, then we can extend this, but this is probably a good place to start the working group felt.

The next thing we talked about was premature infants, and again, the issue about prematurity is much the same. There was concern among the working group and among the ACIP members, judging from the comments from last time, that there was very little data on premature babies. There was a theoretical concern that vaccinating premature babies, especially very young premature babies who had not yet been transferred maternal antibodies, which may be associated with fever or inversely associated with fever would be risky. I think in the October draft you have, because of the concern of lack of data and the concern for higher rates of adverse reactions in young premature babies, they were contraindications for vaccination. That was after the ACIP meeting the last time when people felt that that was probably inappropriate, we changed that in the current draft to make prematurity a precaution, and now in the newest draft, a special situation.

So again, data was presented yesterday. There's still very — there's still no good data on vaccine efficacy or safety in premature babies. There was some data presented again by Dr. Peggy Rennels yesterday and by Peter Paradiso from Wyeth yesterday that the concerns over safety of

vaccinating premature babies may not be warranted. There is some limited data to indicate that these kids don't have a higher rate of adverse reactions, but the data are still very meager. It was finally felt that in light of the meager data, but in the — even despite the feeling, or despite the knowledge that the data to identify premature babies as a high risk group for severe disease is lacking, there was a general feeling that premature babies probably are at a higher risk for rotavirus hospitalization. We certainly know that there are high risks for diarrheal hospitalizations. Because of that, it was felt that these — we should allow premature babies to be vaccinated along with everybody else, but we would provide a precaution, or a word of warning or an explanation of this at least in the statement. Finally, or next I guess — do you want to continue past this; want me just to run through?

MODLIN: Why don't you go ahead.

BRESEE: Okay. I'll run through and I'll pick up speed so to leave you guys with some time. One of the issues that came up again and the ACIP comments was — what do we do about kids who live in households with immunocompromised people? In fact, in the October draft, this wasn't addressed at all. In previous drafts, actually it was addressed, but was taken out pending further discussion. The alternatives that we came up with prior to the working group were either to recommend vaccination for kids living in households with immunocompromised persons; to not recommend vaccination; or to say that they could be vaccinated, but add a precaution or a word of warning. Again, the issue is how likely is the balance between — how likely an immunocompromised person living in a household with a young infant of immunization age is likely to get infected with a vaccine virus and sick from that virus versus infected from a wild type virus and ill from that virus?

It was felt on the balance of data that — and from transmission studies from vaccine study, or transmission from vaccine studies — that the likelihood of transmission of a vaccine virus to a person living in the same household is very small, and that even if they — and the data to say that vaccine virus in immunocompromised person could cause severe disease is nonexistent. There was a feeling that the person was at higher risk probably for illness, and for being exposed to a wild type virus and developing illness during that virus, which has been described as very severe in some cases. So because of that, it was recommended — and I'll show you all the recommendations — but it was recommended that infants living in households with immunocompromised persons should be vaccinated, but again, it's under the special situations part of the new drafts, which are not yet — actually are in this draft, the special situations — and so there's an explanation provided to alert the health care providers of the vaccine, the people who administer the vaccines of the potential risk for transmission of vaccine virus.

There were also four or five ACIP members who raised the question, which we neglected in the previous drafts, of what do you do about administering other antibody containing blood products with this live vaccine? Again, there is no — like a lot of these other things — there's no data on the efficacy or the safety of rotavirus vaccine administered with or without antibody, or with antibody related blood products or the timing near antibody containing blood products. So again, the options were to say you can administer them simultaneously; you can or you can't unless it's — you're going to lose those kids to vaccination, and in which case, go ahead and do it. I think, again, lacking any data, but knowing that there's good data to support use of OPV and oral typhoid vaccine with antibody containing blood products, we elected to recommend or allow vaccination of children who are also getting antibody containing blood products and not to issue any restrictions at this point.

There was a lot of discussion early on and later in the meeting about the potential for adverse effects of vaccination. Really, two adverse effects or potential adverse effects have been brought up in the last year: one is failure to thrive and the other is intussusception among vacinees. The intussusception was discussed, I think, wonderfully by Peggy Rennels two meetings ago here. Failure to thrive, again, was discussed at the FDA meeting in the fall. Both of these data were reviewed yesterday and the feeling — the question was whether we should include something in the statement about these observations that children who were vaccinated developed both these conditions, even though it was the feeling of the working group that they were not associated with vaccine.

It was felt that in the spirit of sharing information, I guess, that we would include sections under the safety part of the text and the recommendations to include discussions of both the data regarding failure to thrive and intussusception in vacinees, and also to include a section that hasn't been included yet on surveillance issues to outline a plan for surveillance of rare or uncommon adverse events. There were a couple of questions brought up by ACIP members about administration of other vaccines. There were really two: one is can you give kids varicella vaccine with rotavirus vaccine? It was a moot point because the decision was made to vaccinate no one past a year of age. So probably, it wasn't discussed at length and is not addressed in the current draft.

Question two was can we say — not can we "day" — can we say no interference with hepatitis B vaccines and IPV? While we couldn't say it on the October draft, there was data presented by Peter Paradiso from Wyeth yesterday to indicate there's no interference when RotaShield is given with hepatitis B vaccine and IPV. So those were included; the statement was amended now to include those in the first line of recommendation number two. Finally — maybe not finally, but almost

finally — there's a, in the October draft, there was a contraindication which said "vaccination is contraindicated for infants with pre-existing gastrointestinal disease." These diseases were — examples of these diseases were given in the recommendations. There was, again, a long discussion of this, I think. It was finally decided to allow vaccination of these children, but provide — again, not a precaution — but a special situations note at the end regarding the fact that there really is no safety and efficacy data in these children, but that the health care provider may want to weigh the risk and benefits of vaccination of these children. So we didn't — it was not a contraindication, but there was a note at the end to allow it if the health care provider thought that the benefits outweighed the risks.

Number nine — we're getting close to the end, and these are short; I promise — there was, again, four or five ACIP members picked up on the fact that we didn't mention what to do if a kid spit out or vomited a dose of vaccine, which was an oversight. So again the options would be to treat it like polio and the recommendations — to agree with general recommendations on immunization — that is if it's the judgment of the person giving the vaccine, that the child spit out most of the vaccine or all the vaccine, to readminister it or the child should not be redosed. Here, I think we differed with the general recommendations. We felt that there was insufficient safety data for the vaccine in giving more than one dose and to warrant redosing the vaccine; and also felt like that in the vaccination studies with a lower dose of virus than 10^4 vaccination studies, the efficacy of the vaccine was very good in American children. So if a child received a partial dose of vaccine, it's probably enough. It may be enough to confer good efficacy in the child. So it was felt that these considerations — and again, the lack of safety data — that children should not be redosed if they spit out the vaccine or vomit the vaccine shortly after administration.

Nearing the end — children with ongoing diarrhea or vomiting. Again, we brought this up mainly to revisit the issue though no changes were made. I think this was listed as a precaution in the October draft and will be listed under the special situations section of the current draft. That is, we left a statement to say that the efficacy of RRR-TV as given to infants with diarrhea has not been established because infants with diarrhea may have a diminished immune response to RRV-TV. There is a theoretical risk that efficacy might be compromised and further studies are needed. So that statement was not changed.

Not quite finally, but almost finally, again, is we will add — though we haven't added — a section to the statement to the list called *Recommended Surveillance Research, Education and Program Evaluation Activities*, in which we'll outline a lot of the needs. As you can see from the review of the recommendations, briefly, there still are a lot of

research needs to establish safety and efficacy in particular groups, whether they're older kids or premature kids, a lot of surveillance needs to detect adverse reactions and detect program effectiveness, and a lot of education needs to educate physicians and parents of the need for rotavirus vaccination.

Finally, here's a list of the new section of the text, which is called *Special Situations*, and the list of things that are included. I've mentioned all of them except for the last and that is *Later Incomplete Immunization*. That was another thing that was discussed yesterday and while. . .

SNIDER: While they wanted to do.

BRESEE: I'm sorry? I think that's discussed in the special situations as well. We outlined recommendations for vaccinated children who missed the 2, 4 and 6 month recommendation vaccination schedule. That, in fifteen, ten short minutes, is a summary of the discussion. Again, I encourage the working group members to chime in about other concerns or discussion.

MODLIN: Thanks, Joe, for summarizing a whole afternoon's discussion in a short, concise period of time. As Joe and Roger mentioned, this draft, of course, has been long in gestation, and despite the fact that it's been long in gestation, it still is — it's still not complete. Nonetheless, the working group felt that we had sufficient information to go ahead and to at least recommend to the full ACIP that we go ahead and discuss the issue of the strength of the recommendation for rotavirus vaccine, and attempt to make a decision at least on that point today. The reason being that we felt that if licensure is anticipated by later this spring that it would be wise to have a statement, at least in preparation, at the time that the vaccine becomes available to practicing physicians. This was a consensus consideration. I should admit that it was not a unanimous consideration, and that there — as Roger mentioned, we think that we have virtually all the scientific data that we will have in the next few months to a year or so on which to base a recommendation.

As some members of the working group pointed out, there is at least one very important piece of information that we do not have and that is what the cost of the vaccine will be, which will be an issue. So the question for the members of the ACIP is do you feel like we have enough information to make a recommendation today, and if not, when do you feel we will have that information — what the sense of the Committee may be? Carolyn, you had your hand up high a second ago. So why don't we go ahead and launch into this discussion? There is a tremendous information that Joe very nicely summarized, and obviously, there are a number of questions that come up regarding issues of age of immunization, appropriate groups for immunization for precautions that we can discuss in much greater detail as the issues come up. Carolyn?

HARDEGREE: This is not pertinent to the recommendations, per se, but I did want just a clarification of the point that Roger made. This was discussed with our advisory committee. They were not asked to vote on whether the product should be licensed or not. They were asked specific questions about the product.

MODLIN: Specifically is it safe and effective, and that was what the vote was is my recollection.

HARDEGREE: That type of question, yeah.

MODLIN: Alright. Neal, do you want to start with number one — the thinking of the Red Book Committee and your own thoughts?

HALSEY: The Red Book Committee is in the process of drafting a statement. Larry Pickering, who's at my right, is the person who's primarily drafting it. We will be having a conference call next week to discuss the results of the discussion here, and to review a number of the issues regarding the vaccine. We have not made any decision with regard to the strength of the recommendation, nor the population that the vaccine should be administered to. I've expressed my thoughts here in this meeting before, and you expressed them at — I mean, my only concern is that we don't have the cost of the vaccine. We do have a ballpark cost and the I think the ACIP members need to decide, just on the basis of the information available, what they can say. It's a bit of a dilemma.

It's really unfortunate that there isn't some systematic way that we could work more closely with the manufacturer because I think cost may also be driven by the strength of the recommendation. The more vaccine that's sold, the lower the price, I hope, that they would say — sell it for. We don't have any way to address this and they don't have a way to tell us the price until it's licensed. So it's a problem that perhaps we might try to decide how we might circumvent in the future.

MODLIN: Let's start, Marie; we'll go around to the voting members first.

GRIFFIN: I just — I'm not a pediatrician, so I talked to a few pediatricians who expressed surprised that this might be recommended for everybody because they didn't seem to think it was a big enough problem. I just want to know if we have any information about sort of what family practitioners and pediatricians think about this, and how they would accept the recommendation to immunize all children.

MODLIN: Anyone who'd like to address — I'm not aware of any public preference polls that have been taken amongst practitioners just yet; inevitably, they will be, but I'm not aware of any scientifically or semi-scientifically

obtained data. Anyone else that can address Marie's question? Wyeth? Peter?

PARADISO: I think it's. . .

MODLIN: I was just — I'm sorry, yes.

DUNN: Yeah. Ruth Ann Dunn, Michigan State University. That was actually a suggestion I made to Roger in writing perhaps to find out what survey data are available, but as one pediatrician, I see a lot of rotavirus and it's a scourge. I am surprised to hear that pediatricians that you've talked with didn't feel it was a big enough problem. At my university, we definitely think so.

MODLIN: Thank you. Other comments specifically regarding Dr. Griffin's concerns? Paul.

GLEZEN: Well, I just got off the service in January in *General Pediatrics* and it was one of the major causes of hospitalization of kids. The thing I want to point out is these kids are not admitted right off the street. They all come into the emergency room; they're rehydrated and they try to send them home, but unfortunately, if they won't keep down oral fluids and they're still febrile, a kid this age, you just have to put him in the hospital because running fever and not keeping down oral fluids means dehydration very rapidly.

GUERRA: I would say in our own community, for example, during this winter season, this probably has been the second most common cause of admissions to the children's hospital of a population that represents a cross-section of the community. I think that it was probably right behind RSV in terms of kids being admitted to the hospital. The clinical syndrome associated with it certainly runs the spectrum from relatively mild to moderate dehydration to those that present in shock and metabolic acidosis, and lapse into a state of renal insufficiency and have a protracted hospitalization. I think over several seasons, one can certainly see that pattern. I think it has certainly its peaks and valleys, but this has been an unusually busy season.

MODLIN: Chinh?

LE: Yes. I'd like to have some comments because I won't be able to vote for this resolution because of conflict of interest because with Kaiser, we are doing other studies with Wyeth-Lederle. So I won't be able to vote, but I guess there's some new ACIP members who were not here when we discussed this. Perhaps what I'd like to do is kind of just share with you my dilemma and basically two questions. The bottom line — if I were to vote for this, I would vote for routine immunization for all children. After saying that, let me just share my dilemma with you. This is my first time

as a “rookie” member here to go through this kind of recommendation for a major vaccine, and perhaps many of you who have been around for the licensing of hepatitis A and varicella vaccine may have some background.

My question is — my dilemma is of the efficacy studies and the safety of the clinical trial, which are conducted in very idealized conditions, would it translate into a similar vaccine effectiveness — efficacy which is effectiveness when used in the real world because most of the cost analyses are based on the efficacy data of very idealized conditions. Then the second part is are we comfortable with cost effectiveness analysis studies done so far, which I tremendously commend Roger for doing; yet, they’re still unpublished. To jump from clinical trials of four or five studies involving about 7,000 children to a national recommendation for 4 million kids, which is a significant economic impact in the private and public sector, are we ready to make that big jump?

Those are the dilemmas in my mind. I know, number one, there will be no new data forthcoming in the future; no vaccine trials, no new studies are pending. More data can only come by using the vaccine in the real field. The urgency, of course, is the vaccine will somewhat be licensed and there must be some guidelines for the practitioners to use. So we’re in a Catch-22. Do we have enough data to support such a national, broad recommendation? Without a recommendation, the vaccine will not be used, and therefore, effectiveness data is not going to be available. If we were to license this vaccine, I think it should be licensed for routine immunization for all children. I would hate to see this vaccine licensed only for the kids who can afford it, meaning the rich parents who send their kids to daycare centers. I would hate to see this vaccine licensed and not having the public funding for the poor kids who have the — who carry the brunt of the hospitalizations and the ED visits. So that’s my dilemma.

The only last comment I have is that the draft here — the last part of the draft did not state some of the areas of further study we would like to include, such as encourage further study of efficacy of two doses, either by case control or by a new protocol. I think that’s very important if cost is an issue. There are some preliminary data that two doses may work as well, especially if you want to just decrease the severity of disease. It’s a third saving for the Vaccine Program.

MODLIN: Chinh, regarding your concern about studies addressing whether using the vaccine in idealized conditions or less than idealized conditions, were you not influenced by the data from the Venezuelan trial where it did look like the vaccine was administered year-round to infants, and appeared to have excellent efficacy — not just like as in the other trials where the vaccine was given only during off-rotavirus season?

LE: Right, but sure, but again, you know, that's one study of, I think, 1,000 kids or something getting that, but when you look at the other four or five studies, for example, the kids did not receive — two studies, the kids were fed formula, one ounce of formula — buffered formula — with 400 milligrams of bicarb or something to increase absorption, and then kept NPO half an hour to one hour after vaccine administration. Most of the studies required the kids are not febrile, not have minor illnesses, not having a family history of diarrhea within three days prior to administration. So that, you know, there is no concurrent disease in the study population. So what I'm saying is those are very idealized, very well controlled efficacy studies. Granted, the U.S. study — the latest U.S. study by Peggy and the Venezuelan study — are broader, just much less restriction, but the data was pooled for all this efficacy study to say that this is the number we're dealing with. I'm afraid that the effectiveness of the study — of the vaccine may not be as high as idealized studies.

MODLIN: I guess I would only take issue with your comment about the data being pooled. I don't believe I've ever seen an analysis in which the data from all the studies were pooled into a single. . .

LE: No. To make efficacy — to make cost effectiveness analysis.

MODLIN: Okay. Fair enough.

LE: Because again, the bottom line is the — if the vaccine is licensed, let's say at whatever magic number sounds to be like $30 a dose or something, it would — it's going to be an equal cost analysis in terms of direct medical cost. Direct medical cost of this disease is about $300 million or so. The cost of the vaccine is $300 million. So basically, so what we are getting in terms of society is the indirect cost of the burden of disease, such as parental wages lost, and daycares and so on. This is somewhat of a new approach to spending public health money, especially if we are only giving it for the rich who can afford it because, you know, whose role is it to pay for indirect society cost? Is it the parents? Is it the insurance company? Is it the public health funding?

MODLIN: Thanks. Rich.

CLOVER: I agree with Dr. Le. I would like to take his comment a step further in the sense that even though the disease incidence is across all socioeconomic groups, my recollection on the data that was presented, the majority of the kids that were hospitalized were in the lower socioeconomic groups. Is that not correct?

MODLIN: Roger or Joe, why don't you address that specifically? It was a big issue — is a big issue.

SNIDER: You need a microphone, Roger.
MODLIN: Hospitalization based on socioeconomic. . .

CLOVER: Hospitalization and death.

GLASS: One that normally thinks of diarrheal disease as a disease of the poor. I think the distinguishing feature of the viral diarrheas are that they affect everyone. I think we've been asked this question — and so Bob Holman is not here — has gone back to some data that we have, state data, and found that one characteristic we have there is race. We found, in fact, that minority races have a lower rate of hospitalization than the majority, but we haven't analyzed that fully. So we don't really have good data on the. . .

CLOVER: I agree that it crosses all economic groups.

GLASS: Sure.

CLOVER: That's not the issue, but I would have sworn the data you presented had a higher rate of hospitalization in inner cities and lower socioeconomic groups because I remember vividly raising the question on your cost effect analysis that the indirect cost that you were alluding to, you used the mean income of the United States and not the disease-based population adjusted incomes, which further skews your analysis in favor of a cost effective outcome. I've asked that question now three times and I've not had a formal response.

GLASS: We really don't have the data on the socioeconomic status of hospitalizations from the data presented. That's from the NCHS database, the basic CDC reference. So I'm not familiar with those.

MODLIN: Barbara, we'll go around first.

DEBUONO: I'd just like to make the comment that I'm a little uncomfortable moving forward with this at this time. A couple of reasons — I think I too hear comments a little bit more along the lines of what Marie has heard in terms of a little surprise in the pediatric community that we'd be moving so quickly so soon on this prelicensure. I like being ahead of the curve; I think that's a great idea. I'm not sure that I understand the urgency this meeting now.

Secondly, I have a little bit of a problem with the notion of the cost benefit analysis in light of not having the information about the cost. I worry about what we're signaling when we say and recommend that something should be given on a universal basis. I think that triggers then a VFC decision that's going to mean inclusion in the VFC Program, which certainly would cover the vaccine for those who are in the Medicaid

program, underinsured, go to health centers, et cetera, but then what do we do about those kids who are privately insured — perhaps in managed care, perhaps in a variety of other private insurance programs where, again, the issue is going to be raised of the cost, and who pays for that and how that gets paid. I'm not sure that we're not going to wind up with quite the opposite effect from what you mentioned, Chinh Le, which is that we'll see the VFC kids well covered for this vaccine; yet, the other populations, perhaps not as well covered. I think I'd feel a lot better with more information about cost.

I think the other question that I have is how much of the issue around both hospitalization and length of stay are related to this whole dehydration and rehydration issue? If that were done — again, more quickly, perhaps in a different manner more effectively — might this cost analysis change a bit? I don't know the answer to that, but I do know that I'm not, at this point, comfortable recommending that we go forward with this.

MODLIN: Okay. Dave?

FLEMING: I think I share Barbara's sentiments on this. I believe that in doing my own internal sensitivity analysis of issues that my recommendation would depend on what the ultimate price of the vaccine turns out to be. In that context, I do think it would be premature for me to say I favored universal or routine for all — I'm not sure what the distinction is; that's pretty subtle. In the absence of knowing the price of the vaccine, I think that we can move forward with all the other aspects of the statement. I think that if the vaccine is licensed between now and June, it would be unlikely that the statement would be ready to go before June anyway. We have an opportunity, I think, to make a more reasoned decision about that wording once we know the price of the vaccine.

MODLIN: Mimi.

GLODE: Well, I have some concerns about the special circumstances, but I'm very convinced about the safety and efficacy of the vaccine in healthy infants. I had assumed that there was not going to be any recommendations made from this Committee before licensure of the vaccine; someone brought that up, but I'm presuming that the recommendations follow. So now I'm only left with the procedural issue of the Committee that do we have a standard or should a standard be established that no vaccine recommendations are made without the cost of the vaccine being presented to the Committee? I doubt that that's been the situation in the past, but are people proposing that situation in the future? Maybe it's been the past standard; I don't know.

MODLIN: Those of you who have been around longer than I have might want to address that, but I don't believe that there's any precedent or any rule that we follow regarding that issue. Walt?

ORENSTEIN: I have never heard that before where we've held the vaccine hostage to a price. I think we've made our decisions on what we feel is the best — in the best interest of children, or adults or both depending on that and we've never let — that has been an issue that we've tried to negotiate afterwards. You can get a cost today and make your recommendation, and the cost can change tomorrow, so that there's no guarantee that a year, whatever the length of the contracts are — so I think that holding it hostage, I think is my opinion, a mistake. I think the — I'm certainly very impressed by, if I recall correctly in the sensitivity analysis, at least with indirect cost, substantial room for cost-related issues and substantial flexibility here. We've got a vaccine that has been demonstrated to prevent diarrhea and hospitalization.

I'm concerned getting any recommendation that might be targeted solely to the poor. There's a substantial distrust out in various communities. Dr. Faggett mentioned the Nation of Islam. I think that the way to go is either universal or not universal, and I think that the data — we will never get enough data to feel totally comfortable. I think we've done it with every vaccine we've gone through. We've always had concerns and I think the need to monitor, follow effectiveness, phase four trials, safety will be needed no matter what is happening.

MODLIN: I know, Dr. Helms, you're new to the Committee and probably new to this issue, but I'll at least give you an opportunity. We've polled everybody else. If you have an opinion. . .

HELMS: Thanks. Although I'm not a pediatrician, I do have — I do echo the same sentiment about the importance of having the cost available at the table now. It really would be nice to be able to answer questions about how will the cost influence its use on the outside, but I — that recommendation really has to come from the Committee itself. I believe that the job of the Committee is simply to decide whether this vaccine is safe, effective; whether it's basically the right thing to do for children or not. It strikes me it is. The universality argument that I'm hearing is very compelling. You can't define your subpopulations to use it in; therefore, you'd want to use it in all children. It cuts across socioeconomic barriers. I would be — I would argue that we don't need the cost necessarily to make the decision here. I think though that the Committee is going to take some heat when it — if it does make a decision along that line. We just ought to be prepared to do it — to take it rather.

MODLIN: Fernando, did I — didn't intend to skip you. You gave a — had an opinion earlier.

GUERRA: No, that's alright. No, that's quite alright. I certainly wanted to commend Roger, and Joseph and the members of the working group for the information that they've brought to us. I feel very strongly that there is enough morbidity historically and a lot of children at greater risk for this disease that regardless of cost, we need to move forward with the recommendation that at least would allow us to begin to get the kind of experience and information that will maybe in the future allow us to modify it some way. To continue to postpone it reminds me a little bit of the dilemma that we faced to a certain extent with the introduction of the varicella vaccine; where it was only after it had been available within the specific guidelines of VFC that we began to recognize the fact that greater morbidity was occurring in the next older age group. So then they came back to the Committee for modifying that.

I had one additional question for Joseph or Roger. In the instance where a young infant has proven rotavirus infection at, say, two months of age prior to the time that the vaccine will have been started, should it be given to that infant? Then the other point or similar question would be in the instance where the young infant has been started on the vaccine, and is maybe four months of age and develops clinical rotavirus infection, should the series be completed?

BRESEE: In fact, that there's language in the new recommendations — if you can hear me — there's language in the new recommendations to address those issues. The recommendations are now that even if a child is diagnosed with rotavirus diarrhea, and the rotavirus is detected by an antigen kit or whatever method, that that child's completed immunization — a three-dose immunization schedule. That's because that a single natural infection doesn't confer complete protection. It confers some protection, but not complete, and that single infection to one of the serotypes confers poor protection to other serotypes. So the fact that a person can be reinfected and become ill the second time despite an infection, and the fact that there's maybe multiple serotypes that circulate within a child's first five years, a child should complete the vaccine schedule.

MODLIN: Do you want to address Fernando's question about delayed immunization?

BRESEE: The same thing — the question was if a child gets — what was the question? If a child gets the first vaccine, then becomes ill?

GUERRA: Yeah.

BRESEE: It's the same answer really, and that is the fact that even if a child gets his first infection from a vaccine virus, the second infection with a wild-type

virus, he still has some protection, but probably not complete and so should continue the vaccination program to get all three vaccines.

MODLIN: Let me open it up if there are other comments on the issues we've been talking about from the wider group. Peter, go ahead.

PARADISO: I had actually two things. The first, I just wanted to get back to what Chinh Le was talking about before in case there's any misconception. The efficacy trials for which the licensure was sought all used the same dose of vaccine, and the same amount of buffer and the same — there have been a lot of efficacy trials with formula and with other things. The efficacy data that you have seen has been using a standard formulation, and it's all the same and the buffer is provided. So there are other trials that the vaccine is used in different ways.

The second, again, the issue of cost — at the last meeting, I made a statement that I know is general that says that the vaccine cost will be within — certainly within the cost effectiveness numbers and within the numbers that you've seen for newly licensed vaccines. The truth is that we don't know the cost of the vaccine. Walt just alluded to that by saying that two-thirds of the vaccine will be sold to the government through the VFC Program or through some program. That price is a negotiated price. We won't know that price until we negotiate with them. They are, obviously, a powerful group and will get the best price, no doubt, but you know, it seems like we're trying to be coy about this. In fact, the price — or the average price of the vaccine that we're going to — that we'll charge to begin with over the next three years, you know, we don't know at this point.

MODLIN: Thanks. Rich?

CLOVER: I'm afraid my comment about socioeconomic groups was misinterpreted by Walt. I'm not at all arguing or suggesting that we should target this population. When we tried this with other vaccines, it has been — it has not worked. What I'm challenging is the assumptions made in the cost effectiveness analysis. If we're going to use cost effectiveness analysis as a measure for making a recommendation, I want to make sure our assumptions in that cost effectiveness analysis are correct.

MODLIN: Thank you. Rick?

ZIMMERMAN: One of the implications down the road is when is this going to appear — and I mentioned this yesterday in the working group — but when is this going to appear on the routine childhood immunization schedule? Is it the 1999 schedule or the year 2000 schedule. I guess, in part, I'd be interested in how quickly would — assuming licensure in the second quarter — how quickly would a contract be in place and vaccine be

deliverable through the VFC system? If two-thirds is going to go through the VFC system, when would it potentially be available?

MODLIN: John?

LIVENGOOD: As you know, there was considerable delay between the licensure of varicella vaccine, development of the statement, and the initiation or finalization — whatever you want to call it — but the contract. I have never actually thought of when it would appear on the harmonized childhood immunization schedule until you raised that question, so I have to say I don't know. If say, May, the vaccine was licensed; June, the ACIP finalize their statement, at that point, our contracts office would initiate a request for a contract to deliver the vaccine. I think as Peter alluded to, the contracting officer of CDC has definite opinions as to based on the cost benefit analysis, based on recent vaccines, based on the fact that she buys millions of dollars worth of vaccine each year on what something ought to cost and when someone's negotiating honestly with her. If she feels that that has not happened, the contract just doesn't ever come to a successful conclusion. It took a year or so for varicella, I would say, waiting for, you know, sort of various conditions and thoughts in the mind. So I — right now, I can't tell you. Normally, it takes three months, I mean.

ZIMMERMAN: I think this is a relevant question because it really indicates if you're saying that it's not available for two-thirds of the kids in the — you know, two-thirds of the newborns. Then do we really want to push it for 1999 schedule, which has implications potential on your timing. Are we saying it is going to be available? I think that's a somewhat critical thing to get into Chinh Le's comments because if it's clearly a 2000 schedule, everything can be sewn up — all the cost effective analysis; everything can be completed, but if it's 1999 schedule, which is what we talked about yesterday, that's going to push things. I guess the question — are the children covered by VFC going to have the vaccine? I think it's a relevant issue.

LIVENGOOD: Well, the children covered by VFC could get the vaccine.

ORENSTEIN: We've put things on schedule and not had them; things get licensed before they're out there; recommendations come out. I think that that's going to happen. Even with the contract, there will be some areas that enthusiastically adopt this and it'll be out there right away. There will be other areas that will do it less quickly than others that may oppose it just like in any sort of recommendation that has ever come out. I imagine that this will be controversial. I don't think I would get all that worried about when to put it on the schedule. In terms of available, I think it's three to six months usually. I think that varicella may not be a good example in the sense that there was a temperature issue, and a distribution issue

that was very different than I understand with this vaccine. So I don't think I would use varicella. Obviously, there could be unanticipated issues.

In terms of a recommendation, whatever you say today, I would presume you would reserve judgment that if new information becomes available in the licensure process, that you would have the opportunity to revisit it. So I don't see yourselves writing this in stone today; nevertheless, I think it would be helpful to have a recommendation so we can alert people that this is coming down the road, and to begin thinking about it and preparing for it even if new information suggests a change later on.

MODLIN: Thanks, Walt. Yes?

WEXLER: I'm Deborah Wexler from the Immunization Action Coalition. Just with the lessons we learned from varicella vaccine in the special handling and storage requirements, I haven't heard any discussion here. I think it would be helpful for those of us who haven't been involved in the clinical trials to hear about how you delivered. It think it's 2½ cc's of a liquid into the mouth of an infant, you know. That's like three Tylenol droppers full. Is there — does this vaccine have to be reconstituted? I mean, what is the nurse's role in this in terms of mixing a vaccine in terms of if it has to be reconstituted, how long can it sit out on the counter before it has to be thrown away? What temperature does it have to be stored at in the refrigerator? Just how do you get it? Has there been a — how palatable is this vaccine? I mean, on a scale of one to ten, how good tasting is it, you know? With the drops of oral polio vaccine, we don't have a problem. It tastes good and it's a couple of drops. So it would help us to get some information about that too.

MODLIN: I think you'll find that most of that information will be in the statement. I believe it now is in the draft statement. Peggy Rennels, do you want to just very briefly — she's probably has had as much experience administering this vaccine as anyone.

RENNELS: Actually, my nurses do, but it's going to come in a little vial — lyophilized vaccine — and there will be this little plastic dispet that has the buffered diluent. You simply squeeze the buffered diluent into the lyophilized vial of vaccine; it immediately dissolves. You suck it back up into that same dispet and squirt it into the child's mouth. They seem to like it. It's a little bit salty and they seem to like it. I mean, do some of them drool? Of course they do.

MODLIN: Roger?

GLASS: I didn't really plan to present any data. I just wanted to show this one slide or overhead, which is the disease burden, because I think the

economic drive for this vaccine — I think Chinh Le put it well — is that the vaccine cost will be awash with the savings and medical cost. The issue that will really drive this is the fact that there are 3 million events a year of diarrheal — of rotavirus diarrhea. About half or 60 percent of which will be prevented with this vaccine — the mild disease — as well as 70 to 90 percent of the more severe events. So we end up with about 2 — a little bit over 2 million rotavirus events ranging at about 3 to 3½ days based on the vaccine studies and longitudinal studies. When you get about 10 million patient days times about $70 per day for a care giver, the real driving force in the societal or the indirect cost of this vaccine and the tremendous savings is going to be in how the parents deal with sick children. So it's the number of children and the social cost or the parents' cost, which is equally if not more important in driving this vaccine than the actual medical cost, which will be canceled out by some of the vaccination cost.

MODLIN: Further discussion? Yes, Dr. Nichol.

NICHOL: I know for myself I continue to debate with myself the relative importance of direct and indirect costs. I would, however, just comment that cost effectiveness does not require does not cost savings. I'm not sure how many of the vaccines currently included in the schedules actually result in cost savings. I think they're all highly cost effective. So that's just a comment. Maybe they're all cost saving; I suspect not. Sometimes, it's useful to look at numbers of people needed to be treated in order to prevent an outcome. It looks to me like you only need to immunize 100 kids to prevent one hospitalization.

MODLIN: It's about 78.

NICHOL: Well, if the vaccine is 80 percent effective, so it's probably about 100 kids.

MODLIN: Thank you.

SNIDER: I would like to comment about indirect cost from a policy standpoint. CDC has visited this and we clearly — as I think the rest of the federal government, or at least the rest of HHS agrees that we should be looking at these issues from a societal perspective, which means that indirect costs are of concern to the government. It's clear that there are other perspectives that people can look at this from a standpoint of their particular health care system or what have you, but from our standpoint, the indirect cost should be of concern and counted as a liability that is on society that we should try to alleviate.

MODLIN: Further discussion? Rick?

ZIMMERMAN: Just a comment on the number needed to treat — I did some "back of the envelope" calculations. In terms of illness perspective, it was 2.5 to 1, which is pretty favorable. In terms of hospitalization, 78 to prevent 1 hospitalization. So you're pretty correct.

MODLIN: Any additional comments from anyone in the room? If not, I think what I'd like to do would be to actually get a vote from the members of the Committee — voting members as to whether or not they want to make a recommendation today. That would be the first vote and so I guess as the Chair, I will make — call the question as to whether or not we do wish to vote. Mimi?

GLODE: Aren't we voting on language in the proposed — in the statement given to us, which would; I mean, are we. . .

MODLIN: Well, I think the first thing would be to decide whether or not we want to make a decision and then the second vote would be — and the discussion would be what the language would be, what that decision will be. Does that seem reasonable?

GLODE: You're not planning to recommend an unlicensed vaccine? You're preparing a statement, but you're planning to then approve and distribute immediately following licensure?

MODLIN: At some point after licensure, correct; at the time, yes. Okay. Could I ask how many members would vote yes to say if you — are you prepared to make a recommendation today? So Chinh, I'm not certain whether you can vote here or not if you've already recused yourself, but probably in the interest of. . .

SNIDER: Call them.

MODLIN: Call the names, okay. So in favor — Guerra, Clover, Griffin, Modlin, Helms and Glode. Opposed — DeBuono and Fleming. Okay. I think the next thing, Joe, would be to put up the overhead with the various options that were considered by the working group yesterday so that we have a range of possible options to consider. I think I can say that the clear consensus of the working group was that if we do make a recommendation that it contained the language under Option B, which actually recommends routine immunization. If you strike out the word "universal," I think the word "routine" is closer to what is generally used with most ACIP and Red Book recommendations.

BRESEE: I apologize. We don't have overheads with the exact wording that's listed in your hand-outs. Oh, I'm sorry; we do have wording.

MODLIN: Roger, let's hang onto that hand-out because there were other options for language to consider and I think — and I guess the thing to do now is to open up the discussion to just this point as to what the relative strength of the recommendation should be. Is there anyone who considers that it should be other than what the working group recommended? Dave?

FLEMING: I have a question.

MODLIN: Yes.

FLEMING: In looking at other ACIP recommendations, what is the language for universal or routine? I mean, I don't — I think at a minimum, I would be in favor of language that is unambiguous. One way to make language unambiguous is to make it match the language for the previous statements. So what is it that the ACIP usually says?

BRESEE: Yeah. That's why we initially said "universal" on the last draft. It was pointed out to us by the veteran members of the ACIP that universal is not a word that's used in ACIP language. So the usual ACIP language would say — and correct me if I'm wrong — something more like this: "The ACIP recommends routine immunization."

SNIDER: I would also point out that that's important for the linkage to VFC because we distinguish between vaccines that are given to children routinely as opposed to in special circumstances or VFC coverage. So "routine" has a special meaning for us.

LIVENGOOD: We do this in the National Vaccine Compensation Program. VFC can be whatever you say it is. There would be no difference in VFC coverage, but B or C, either one could be linked in a VFC resolution to provide that either it's routine or it's not. It's just when you get to the Injury Compensation Program. . .

SNIDER: Yeah. Well, I was going to say that.

LIVENGOOD: . . .they're much tougher about getting through the door with "routine."

SNIDER: Well, we haven't gotten to our policies and procedures from tomorrow, but the word we're using for — if we accept those, the word we're using for inclusion in VFC in our policies and procedures is "routine." So if we adopt that, then it will have special significance.

MODLIN: I'm going to ask Geoff Evans if he has a preference? Geoff?

EVANS: No. The only thing I'd point out is the language that was in the legislation is what CDC recommends. It should be for routine administration of children. So in other words, it's your — ACIP comes up with specific

language, but it's what CDC publishes and for recommendation for that purpose.

MODLIN: Chinh.

LE: I'm very afraid of Option 2 — I mean, C or D. If you say that recommendation should be considered or believe to be appropriate, that really gives a lot of leeway for insurance companies, HMOs and so on to say, "Well, we'll do away with it for now." I think that would then come down to an unethical program in terms of who gets a vaccine and who doesn't. I think it should be either we don't make a recommendation or we should make a recommendation for routine immunization. Otherwise, some kids will get it and some kids won't, and that's not fair.

MODLIN: For the sake of completeness, I'll just point out that we did have one other alternative, which came between C and D with the effect that recommends that immunization may be considered — a slightly less strong recommendation.

BRESEE: We mentioned that earlier.

MODLIN: I don't mean to be splitting hairs.

LE: That's still a loophole.

MODLIN: This is Option C(1) or C(A).

BRESEE: C.

MODLIN: C(1).

BRESEE: C, sub 1.

MODLIN: Further discussion?

BREIMAN: John?

MODLIN: Yes, Rob.

BREIMAN: There is — another thing we haven't really talked about is potential implication as to the type of research that can be done in the future. I guess, you know, obviously the best type of research is done in sort of a prelicensure or at least a pre-recommendation phase where you're able to do control studies and so forth. I get the feeling from Roger and Joe that we've answered most of the key questions, but some of the things that have been talked about today, like looking at two-dose regimens and maybe doing demonstration effectiveness-type studies would be more difficult, at least, to do if you have made a declarative, you know, routine

recommendation sort of thing. Then you'd have to use the, you know, the other methods that we have to rely on that are not necessarily as clean.

MODLIN: That's a good point, but I think Joe did address that in the last part of the statement. There's no question that the intent is for the statement to follow — the usual routine would be to have it, to complete the statement with a section on recommended studies for the future. There were a number of important ones that came up. I don't think we're going to have any difficulty. Roger, do you want to. . .

GLASS: Well, as good researchers, there's never a study that's done that you don't have other questions. I see a lot of very important questions that still need to be addressed, such as the two-dose regimen, which we will — with a seasonal disease like this, we can certainly assess by looking at children in December who have had — children of the same age who have had two or three doses and who then go through the season. Through the VSD project of CDC, we have the option to address that. We have the option to look more carefully at these low risk adverse events, like intussusception or failure to thrive. So I think that we have ample leeway when we get into larger studies to address those questions. We're interested in surveillance of strains as well. So there are lots of questions, but I think those could be well addressed in the phase four follow-up.

BRESEE: Yeah. I'd echo that, I guess; that we had — the working group had recommended a section be put in the statement to outline some of the study needs and the research needs, which we haven't had an opportunity to do yet, but will. I think most of the important questions will likely be answered, be able to be answered post-licensure though. As you say, that may not be the way we do it in the perfect world.

MODLIN: Further discussion? Could I hear a motion from the Committee if that's the case? Mimi?

GLODE: I vote to move that recommendation be fully adopted.

MODLIN: Okay.

GLODE: Alternative B.

MODLIN: So it's for adoption of alternative B with the language being "routine immunization."

GLODE: Recommends routine immunization.

GUERRA: Second.

MODLIN: It's a second from Dr. Guerra. Further discussion on this? Those in favor of the motion, raise their hand. In favor — Guerra, Griffin, Modlin, Helms and Glode. Those opposed — Clover. Those abstaining — Le, Fleming and DeBuono. Motion carries. What I'd like to do now is to get some discussion around the point of age of immunization, specifically, immunization for infants that are older than six months of age. You heard Joe present a summary of data, although I don't think we've presented the data to the Committee regarding possible increased risk, particularly of febrile reactions in infants who receive this vaccine — who receive their first dose of vaccine at five months of age or greater. I think it might be worthwhile reviewing those data and then having a brief discussion. I don't know whether, Joe, you want to do it or Dr. Rennels would be willing to discuss the issue.

BRESEE: If Dr. Rennels is willing to do it, I think she would — it would be best for her to.

RENNELS: Can you hear me? The very earliest trials of the rhesus rotavirus vaccine were done with a dose of 1×10^5 of the parent rhesus rotavirus. That is, of course, one of the four components in the tetravalent vaccine and is the same dose. These first trials were done in children between five and twenty months of age. One of the very earliest was done at the University of Maryland by Ginnie Losonsky and me. You can see that among the vacinees, seven of fourteen had a rectal temperature of 100.6 or greater, as opposed to two out of thirteen controls. Now of those seven fevers, five of the fourteen were greater than 102 versus zero of thirteen of the placebo recipients, and that difference was significance.

I did home visits and I examined all of those children with fevers. They were not happy campers; they were not playful kids with fevers. Now simultaneously, it went on in Sweden and in Finland — other trials of the rhesus rotavirus vaccine at $1 \times 10^{5.}$ In both of those trials of the same age, five to twenty months, the majority of those children experienced fevers — many of them high fevers. It was really thought that that was an unacceptable reaction. That then led to all of us doing trials of lower doses and comparing the febrile reactions when you gave 10^3, 10^4, 10^5. There wasn't a great deal of difference by the dosage variation, but I looked in my group at a breakdown by age. I was able to show that children vaccinated — this one dose of vaccine given before five months of age, there were no febrile reactions; whereas, the children over five months of age, seven of twelve had febrile reactions and that difference was significant. It was, I think, in great measure based on these results that the decision was made that vaccinations would be given then at two, four and six months of age.

MODLIN: Questions for Dr. Rennels? Comments? Mimi?

GLODE: In the trials that you mentioned in Europe that also showed the fever, when they broke it down by age, did they show the same thing?

RENNELS: No, they didn't. No, in fact, I. . .

MODLIN: Peter, this might be an opportunity for you to show the fever information from the control trials that is broken down by age with respect to first dose.

PARADISO: Is that mike set up? Can you hear me? The vaccine that was tested, unlike the monovalent vaccine, this is the tetravalent vaccine. In the context of the trials, and actually, the decision was made at that time to keep the primary vaccinations under six months of age. So all of our data is under six months of age. That's the reason that the indication certainly would be for six months of age. There was significantly more fever in Finland in all ages, and greater than 38 or greater than 39.

We looked at the data from the U.S. trials. This is the trial from — this is the U.S. efficacy trials from the multi-center trial plus the Navajo trial. If you look at excess fever on the Y-axis — and this is fever greater than 39 degrees — and you look for excess fever of the vacinees over the placebos in those groups, you can see that the excess fever is not significant in any case, but in the five month old, it does go up. I have to warn you that in the five month, and that's up to six months of age, there were only two fevers in that group because the cohort was so small. So the majority of the kids did get vaccinated by four — before four months of age in the first dose.

MODLIN: This is first dose?

PARADISO: This is first dose, yes. There was no difference in the fevers after the first dose.

GLEZEN: So what you mean is that also after the first dose before five months, it was very unlikely to have excess fever?

PARADISO: Right.

MODLIN: Fever over 39.

PARADISO: Right, over 39.

SPEAKER UNIDENTIFIED: Were these rectal temperatures also?

PARADISO: These were — in the U.S. multi-center study, these were axillary temperatures and in the Navajo studies, they were rectal. There's about an equal number in those two. Again, as I said, the contribution of fevers

in the database from Finland is significantly higher and I think you've seen that data. I didn't go through all of it. This is the U.S. studies.

MODLIN: Questions? Let me point out that the revised statement reads that "the first dose should be administered at age two months. The second and third dose is administered at age four and six months, respectively. However, rhesus rotavirus vaccine immunization may be initiated at any time between age six weeks and six months with the second and third doses following the preceding dose by a minimum of three weeks. Because infants greater than six months of age may have an increased fever occurring approximately three to four days after receipt of the first dose of vaccine, initiation of vaccination after age six months is not recommended. All doses of vaccine should be administered during the first year of life because data regarding the safety and efficacy in children older than one year are lacking." I don't think we have this language to project, but does anyone have any concern about using language of that nature in the statement?

BRESEE: It appears that somebody brought up two salient features of the age — of the age cut-offs, and it should be identical to the draft.

MODLIN: Okay. Fair enough. I wonder if we shouldn't just address very quickly the issue regarding immunization of infants who were born prematurely. There were a small number of premature infants included in the trials. Again, Peter, maybe you could show us the overhead that you showed us yesterday regarding the number of infants.

PARADISO: The entrance criteria for the trials was that you had to be healthy at the time of immunization. So gestational age was not a criteria and the data was not collected as such. However, during the course of the trials, there were notations on seventy charts that the child that was being immunized was premature. Then in a total of seventy cases that occurred — let me make sure I get my numbers straight — seventy total, 33 of those were placebos, 37 of them were RotaShield vaccine. Within those, there was a subset then in which they actually indicated the gestational age.

So what this shows you is that the unknowns are the ones — we made a note that they were premature, but didn't note the gestational age. The remainder shows the gestational age of the kids and the number of kids in a group. You can see, obviously, that for each age there are not a lot of kids, but it goes down to about 27 weeks of age — the majority being in the 32 to 36 week of age. There was no difference in the adverse reaction rate, either primary or secondary in those kids compared to the overall population, which was predominantly term we presumed. Now, you know, we don't know whether these were the only kids who were premature in that population or not since it wasn't — if it wasn't noted on the chart, we wouldn't have collected that.

MODLIN: I pointed out that we've had a very hard time as a working group identifying data to indicate that premature babies are a special risk group for rotavirus disease. Interestingly enough, although you find statements that affect here and there, the information to support that statement, interestingly enough, is just not there. So therefore, what we had planned to do was include under the section of *Special Situations* the very first point — point one addresses immunization of premature infants.

It says specifically that "infants born prematurely can be vaccinated if they are at least two months of age and are no longer hospitalized or as they are leaving the nursery. Data are insufficiently determined if premature infants are at increased risk for rotavirus hospitalization during the first year of life, or to fully establish the safety or efficacy of RotaShield in this group. The lower level of maternal antibody to rotavirus is among premature infants might increase the rates of severity of adverse effects of the vaccine, but could also improve the child's immune response to the vaccine. Studies of rhesus rotavirus vaccine in premature infants are urgently needed. Any discussion about this issue? Mimi?

GLODE: I counted; it equals 28. So I would conclude the data are insufficient with regard to safety or immunogenicity in premature infants to recommend this vaccine for premature infants. I don't think it's necessarily contraindicated. I don't see how you can recommend it. "Can be vaccinated" is a recommendation.

MODLIN: I guess the working group was swayed by some information that, again, Dr. Rennels — Peggy Rennels — showed us regarding the risk of naturally occurring rotavirus disease in premature babies. The suggestion that, based on a study of an outbreak of rotavirus disease in the intensive care nursery at the University of Maryland, that the morbidity of rotavirus disease itself is surprisingly small. Again, Peggy, would you mind presenting that information and see if that. . .

BRESEE: As Peggy comes up here, the other thing I would say is that though we don't have any studies to show that prematurity is a risk factor for rotavirus hospitalizations, our studies of diarrheal hospitalizations in young kids do show that prematurity is a risk factor for hospitalization in the U.S. for diarrhea. I think that, again, though there's no data, I and Roger, I think — I don't know if I can speak for the working group — were impressed that it wouldn't take much to convince us that if you have diarrhea in that age group, and if diarrhea is a risk factor for kids under two that are premature or under one that are premature, that rotavirus would also be a risk factor though there's no hard data. The NCHS data doesn't have rotavirus specific codes, and so we were unable to say that actually rotavirus is a risk factor.

RENNELS: There was a rotavirus nosocomial transmission study conducted by Karen Cotwahlf, Ginnie Losonsky, Pablo Vialb at the University of Maryland, in which over two seasons — rotavirus seasons — they collected stools from children every other day on our infant ward, including the previrus step-down unit, which was a room off of our infant ward, which turned out not to be a good idea. I do not recommend that. The same nurses and physicians cared for the same children. So when the community experienced rotavirus diarrhea, community strains infected premature infants who were in our preemie step-down unit. I just went through and listed children by chronologic age and whether or not they were symptomatic or asymptomatic. I was very surprised to see that in spite of very low gestational ages, presumably resulting in little to no maternal antibody protection of these children, indeed, most of them were asymptomatic.

Then looked at — this is — looked at the proportion of children with nosocomial rotavirus infections that were symptomatic by gestational age, and compared it to the premature infants to the full-term infants. You can see 21 percent of the premature infants versus 46 percent of the full-term infants developed symptoms of diarrhea from their infection. Looking then at the proportion of the nosocomial rotavirus infections that were symptomatic by chronologic age, you can see that whereas gestational age didn't seem to be a factor, chronologic age definitely is a factor; that in children after their four month birthday, you get much more symptomatic disease when they develop nosocomial infection.

MODLIN: Thanks, Peggy. Mimi, do you still feel that — I'm sorry; did you have follow up?

GLODE: No. I'm still — even if you could establish with large numbers that these infants were at higher risk, that is not the same question as have safety and efficacy been. . .

MODLIN: Right.

GLODE: . . .safety immunogenicity, let alone efficacy been established in this age group. I think it hasn't and I think it has to say that. I just can't — I couldn't support this recommendation.

GRIFFIN: Could I ask you a question? Do you have any reason to believe it would be less safe or less efficacious? Is the experience with oral polio or other viruses helpful here? Are you concerned about specific safety?

GLODE: Yeah. I'm concerned about it just like the sentence said here that "the lower level of maternal antibody might increase the rate or severity of adverse effects of the vaccine. I mean, I don't have any information because there isn't any information, I guess, but I'd just be concerned

that without establishment in this risk group that you should withhold a recommendation until the data are available, and then you make a recommendation for or against it depending on whether it's safe and effective or not.

MODLIN: Okay. How do others feel about this because this is an important issue that the working group has struggled with, and after struggling with it has basically come down with the language you see in front of you. Dave?

FLEMING: Can I just ask for some clarification of what the working group meant? I think the sense I get is that you wanted to fuzz it a little bit, and you were successful in my mind because I'm not quite sure what this means. From a picky standpoint, "can," I think, might be the wrong word to use from an English standpoint. That just means "it's possible" they do vaccinate so I'm not sure. Did you mean "should be" or it "should be considered?" What was your intent there?

MODLIN: Well, that's a good question. I think the intent was to be permissive, quite frankly. Given the data that Peggy has presented, that the likely — that natural rotavirus infection does not appear to be especially virulent in infants who don't have much in the way of passive acquired maternal antibody because of the age at which they are becoming infected; that the likelihood that an attenuated rotavirus would cause disease would be low; and that that information needs to be weighed against whatever potential benefit there may be from immunizing these infants and preventing disease. It looks like it begins to occur at about four to five months of age in this group. I should point out that we're not going to have a lot of — from the best of my knowledge — any new information on this in the next few months. While we still feel the need to make some sort of a — provide some guidance to clinicians for immunizing infants who are premature, then this seemed to be language that was appropriate, but again, this is a proposal and I'd be very interested in what others — how others feel about it. Jane?

SIEGEL: With the lack of data, is it likely that the vaccine will be licensed for use?

MODLIN: Well, that's a good question. Carolyn?

HARDEGREE: Well, I think that was one of the questions that we asked our advisory committee to look at. We are still looking at all the data that we have.

MODLIN: How do others feel about this? Chinh, you're the — I'm sorry, others pediatricians on the Committee. I'm sorry; Marie, why don't you go ahead? Yeah.

GRIFFIN: Well, I was just wondering if we could just put "some experts believe the benefits outweigh the risk," rather than making a recommendation?

MODLIN: Okay. Neal.

HALSEY: We do that in so many different ways, at least on the Red Book Committee. . .

MODLIN: Yeah.

HALSEY: . . .where we don't have data to make a definitive recommendation, and then we just — I would indicate even within the statement that "the limited available data do not suggest an increased risk of severe rotavirus diarrhea in children who have been infected." The situation at Maryland may have been only with one or two, or Peggy told us the number of strains. So you don't have enough information to be definitive about the severity of disease, but the limited data do not suggest an increased severity from natural disease and that, you know, only 28 children who are defined as being premature have received the vaccine and there were no unusual adverse events in those children. Then either the "some experts" — that's a lot of our language that we use all the time — "believe that the benefits outweigh the theoretical risks," or that then you put the onus on the practitioner to say that they "must weigh the theoretical risk against the perceived benefits" — something like that. There's lot of language to draw upon from the Red Book. We probably say those things about 100 times.

MODLIN: Right. How does this work in a public health immunization program to have language such as this? Dave? Barbara?

DEBUONO: Well, I personally find it objectionable to make a recommendation affirmatively towards vaccinating without any data at all. I'm really more on where Mimi is in terms of thinking. If we're going to issue recommendations about its use in premature infants with this total lack of data, I would just — knowing that if the statement were to read that it "can be used," or it "may be used" or "the risks outweigh the benefits," knowing that there was no data to back that up, I would say let's not use it, but not everybody is going to know that. I don't think it's really responsible of this group to go ahead and make that recommendation without any data at all.

MODLIN: Okay. Other opinions?

SNIDER: That does mean that we'd have to go back to your initial recommendation and put your words back in about term infants, and defining that as greater than 37 weeks.

MODLIN: Right. Larry?

PICKERING: I agree it's always nice to be data-driven when making recommendations, but on the other hand, this recommendation does not mean that we're putting these infants at a greater risk because they clearly are going to — many of them are going to acquire rotavirus and subsequent disease from that rotavirus. So the risk benefit of whether or not not making a statement would harm these infants also needs to be considered.

MODLIN: Okay. Chinh?

LE: To clarify that perhaps, you know, using on Table 19 — page 19 — including premature infants and give it the level of evidence III(C) may just alert whoever wants to use it that this is expert opinion with no restriction evidence and put it — but I think that the question needs to be addressed because if we don't address it, the phone will ring about whether we use it or not.

MODLIN: It has to be addressed; there's no question about that. In the interest of time, does anyone else have a strong opinion about, or any opinion about the premature issue? Dr. Faggett?

FAGGETT: Yeah. Walt Faggett, National Medical Association. Whatever we do, I think we need to really address the issue of trust. I think the more honest we can be, the easier it's going to be for us as inner city pediatricians to convince higher risk patients, you know, that it is safe for them to take it.

MODLIN: Right. Well, the Committee is going to have a chance to revisit the issue again, of course, when we vote on the final statement, which hopefully, won't be too far off. We do need to provide some guidance to those of us who are writing the statement. Let me ask for an informal — well, let me ask for a vote on this in terms of at the moment, those that would recommend that we recommend that RotaShield not be used in premature infants? I guess for premature infants, we would have to define those as less than 37 weeks of gestation; the alternative being some sort of permissive language or language along the line that Neal had mentioned — Red Book language that's sometimes used, which is that "some experts recommend."

DEBUONO: You're sort of leaving it up to the practitioner.

MODLIN: And then — yes, it would be leaving it up to the practitioner. We'll have a chance to revisit this. This is not a final vote because we obviously will have to vote on the language once that language is crafted. I don't want to take the time to do that now. Let me ask how many members — voting members of the Committee would support a recommendation that RotaShield not be used in premature infants? Can I see a show of hands? We make a recommendation against the use.

GLODE: So you're going to call that a contraindication. . .

MODLIN: A contraindication.

GLODE: . . .versus a non-recommendation? See, that's different to me. "Data are insufficient to recommend its use in premature infants" is different to me than "it is contraindicated."

MODLIN: I guess my point is we're going to have to address the issue in the statement of the use of this vaccine in premature infants. We're going to have to say something. The question is what are we going to say? Are we going to say it should not — "until further data are available, the vaccine should not be used?" Are we going to say insufficient data are available and at some — something along the lines that "insufficient data are available to establish the safety and efficacy, but some experts recommend that the vaccine may be given or can be given safely?"

DEBUONO: I think that's okay. That's different than what the statement is right now in here. I think there was just objection to what the statement was that was in here. I think your modification is reasonable.

MODLIN: So okay. Let me — Roger, first.

GLASS: Two quick comments on this — this is a figure that we presented before. One of the issues that made it difficult to define prematurity were the numbers and the age. When we were thinking about this earlier and we presented this, we weren't sure at what cut-off of age. This actually gives us the number. The other thing that's motivated us in thinking about giving it to premature children are two studies that we've done here. One is that hospitalizations and deaths are more likely to occur for diarrhea — more likely to occur in premature children. We don't know if that's rotavirus-specific enough, but diarrhea in general, these children have a poor constitution or whatever, but they're at greater risk for severe disease. So this will give you the numbers. If you're think about premature and its definition, we can actually put numbers of children who you would be excluding.

MODLIN: David?

FEDSON: Just a question to clarify, at least in my mind, the meaning of immunizing premature infants. Do you mean by the language that a child who is born prematurely should never be immunized or when, after having been born prematurely, should vaccine be given and how much delay should there be before the vaccine is given? I think if you use the statement that "children born prematurely should not be vaccinated," I mean, that implies, and perhaps to some, that they should never be immunized no matter what age they achieve. I don't think you mean that.

MODLIN: Since we are recommending initiating vaccination only up to six months of age, I think for all intents and purposes, yes; that means if we were to make that statement that we would say that "until further data are available, premature infants — infants born prior to 37 weeks of gestation should not receive this vaccine."

FEDSON: Should never receive that information — never receive that vaccine?

LIVENGOOD: But John, I mean, that's not what you said just before.

SNIDER: The sense I'm getting from the group. . .

FEDSON: I think you've got to get very clear on that. . .

SNIDER: . . .is that they want to get data.

FEDSON: . . .because some people might say, "Well, why don't you simply delay if the child is born five weeks prematurely? Why don't you just delay the vaccine for another five weeks beyond what might have ordinarily been with normal gestation two months at a time?" I mean, by that calculation, almost every premature infant who is still surviving will be able to get at least the first dose of vaccine before the fifth month of gestational age after what might have been a normal time of delivery.

MODLIN: I think you're right, but the point is we have no data to support that practice. That's the problem that we're getting hung up on, or very little data.

SNIDER: What I'm hearing from the group, I think, is that the data need to be presented and that — well, the fact that there are insufficient data on the safety and efficacy issue. There is the issue though of increased risk at a gestational age of around five months. Those facts need to be brought out. The bottom line is that, I think, is the permissive — some kind of permissive statement that the practitioner, again, has to weigh, you know, the risk and benefits and make a, you know, make a decision for individual kids because I don't hear a strong sense of wanting to prohibit it, but I also sense a reluctance to encourage it, you know, with the lack of data. So that I hear the Committee wanting to go the middle road so that they don't preclude it, but don't boost it either.

MODLIN: It sounds to me like we've come full circle.

SNIDER: That's what I'm hearing, I think, from you folks.

MODLIN: Okay. It sounds to me like we've come full circle on the issue.

SNIDER: So the exact words you use to express that, you know, need to be crafted.

MODLIN: Okay. Unless there are strong objections, what we will do is we will try to craft some appropriate language and have an opportunity to revisit this when we vote on the statement. David?

FLEMING: Just a point of clarification — is what you're hearing going to change or not change the overall recommendation to put the word "term" in or not? I mean, that's. . .

MODLIN: I'm sorry; change the. . .

FLEMING: The initial recommendation about whether all infants should get this or all term infants.

SNIDER: To me, at least from a logical standpoint, it has to. . .

FLEMING: Yes.

SNIDER: . . .because you can't — it would be internally inconsistent if it did not change, if you did not change the original statement about term infants because otherwise, you're just going to two, four or six months of age and you're talking about both premature and term infants unless you qualify.

MODLIN: Okay. I think we've covered the — Mimi, yes.

GLODE: I just wanted to say that at least even for myself, a post-licensure study of premature infants for safety and immunogenicity — not a $1 million efficacy trial for post-licensure, multi-center trial — would accumulate 500 premature babies for safety. Immunogenicity allows one to then change that, revise it, recommend it.

MODLIN: That's on the list. Further comments? If not, we'll adjourn until tomorrow morning. Before everybody rushes for the door, the first item on the agenda is actually meant for leftover issues, and I'm happy to say I don't believe that we have any. So that if it's okay with everyone, we'll start the meeting at 8:30 tomorrow rather than 8:00. See you tomorrow.

[*THE ACIP MEETING ADJOURNED ON FEBRUARY 11, 1998 AT 6:00 P.M.*]

MODLIN: Yesterday, in my zeal to get started on time, I neglected to ask the liaison members to introduce themselves. I wonder if, for at least those of you who are here, if you would mind going around very quickly — those who are seated at the outer/inner table — and introduce themselves. Then we'll get started with the rest of today's business, maybe starting with Dr. Gilmet.

GILMET: Greg Gilmet, representing the American Association of Health Plans.

SIEGEL: I'm Jane Siegel, representing HICPAC.

GALL: Stan Gall, representing ACOG.

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

FAGGETT: Walter Faggett, representing the National Medical Association.

SANTOS-PRECIADO: José Santos, representing the Mexican Child Health and Immunization Council.

NICHOL: Kristin Nichol, representing the Department of Veteran's Affairs.

TRUMP: David Trump, representing the Department of Defense.

HARDEGREE: Carolyn Hardegree, representing FDA.

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

MODLIN: Thank you. Dixie, do we have any additional business that you'd like to bring up?

SNIDER: No, I don't.

MODLIN: Good enough. Well, if that's the case, then we'll start with the first item. Chinh? Turn on Dr. Le's mike, please.

LE: Thank you. This is Chinh Le. I'd like to ask you a question about the vote — on the vote of rotavirus yesterday if possible. Let's say that, for example, the rise of the vaccine turns out to be just too high, or the Academy of Pediatrics withholds any recommendation. What are we going to do in June or in October? My feeling is that this is such a pediatric disease that unless we really have consensus with the Academy of Pediatrics and we have — or we have divergent issues, I mean, recommendations, it's going to such a chaos and a problem, and a credibility problem that I really think that we have to take AP consideration

at some point in time. Whether, you know, we don't have a final draft now yet. Perhaps if the price turns out to be excessive and the cost analysis changes, is it possible to bring this issue back?

MODLIN: Sure. It's always possible to reconsider a vote. I would point out that we don't have a final statement. It's my hope that we will be able to consider and vote upon a final statement in June. I think the statement probably will be complete to the point that the Committee can vote on the statement itself. We still have a number of unresolved issues, but we sort of tackled the most difficult yesterday, but there are a number of issues that will be in the statement that will need to be discussed. So I think there will be an opportunity to revisit this, if necessary, but on the other hand, I think we — the majority of us felt it necessary to provide some guidance to those of us who are writing the guidelines to get through the issues that we did yesterday.

SNIDER: Also, we want to point out we also see in the policies and procedures that we've clarified for the Committee something that's been true for all the years, and that is that the recommendations that come out in the MMWR are CDC recommendations. So CDC has to accept these recommendations for them to be published in the MMWR. Therefore, again, our pattern — and just as with the polio situation — is not to say to the Committee, "Well, we're not going to accept your recommendation. We'll do something else," but enter into a dialogue with the Committee about the new information or concerns that CDC management might have. So I think the point, again, is just to build on John's point about the fact that there is going to be a revisitation in this Committee of the issues in June, and then with the publication subsequently coming down the pike of, you know, what you folks have put together, there are still opportunities before it goes on the street that there's new information that comes to our attention to re-engage the ACIP if the need were to arise because of concerns.

FAGGETT: John?

MODLIN: Dr. Faggett?

FAGGETT: Yes. I was unable to talk with Dr. Jessie Sherrod. Did you have a chance to get any input from her from the National Medical Association?

MODLIN: Jessie did call last night. I spoke with her late last night. She unfortunately was not able to listen on the proceedings after the break, which included the rotavirus session. She was with us for most of the rest of the day, however. We did have a — I basically filled her in on the discussion that came before the Committee and the Committee's votes on the topic. She did express the fact that if she had been here and had the opportunity to participate in the proceedings, that she would've voted

no on the first item regarding routine use of rotavirus vaccine. She did not have a vote on the second issue regarding — that we discussed regarding premature infants.

FAGGETT: As Dixie said, when the National Medical Association will have an opportunity to revisit this, I'll give her the benefit of what I heard here. So we will be giving you some feedback later on.

MODLIN: Sure. I'm certainly hopeful that she'll be here at the next meeting as well. Okay. Let's move on, please. The first item on the agenda this morning is a report of the work group on computerization of the ACIP recommendations. Will it be Dr. Blumen leading the discussion? Dr. Kilbourne.

KILBOURNE: Can you hear me? Okay. It'll be Dr. Ed Kilbourne to start. Okay. It's a pleasure to be able to speak to you again. What I have for you today is in the nature of an update. Despite the best of its intentions in trying to match schedules, the work group was going to meet for a face-to-face meeting and just wasn't able to pull that off. So we have a series of telephone communications that have gotten us, I think, somewhat further along and certainly further enough along to present some things what are — which we hope are stimulating and should perhaps result even in some debate.

You have in your packet a document that was intended as the basis for discussion of the — I understand were distributed to you; one of them was intended as a work group document and had, I think, seven issues on it. We can't get to all seven issues today. Specifically, there's also included a practitioner's guide, which is an educational tool which we are developing. We feel that physicians and other practitioners who give immunizations that are going to be using computerized systems will want to understand those systems, have a need to understand those systems. We have a responsibility to explain how they work and how they function.

So we give that to you for your information and welcome your comments. If that eventually becomes authored by the Committee, so much the better. The other items that we'll gloss over — but I want to mention just because I think they're important and we will ultimately, I think, be getting to you with a recommendation — are the issues of small differences. We mentioned these before. They have to do with precision in the recommendations and the timeliness in which the recommendations are given. Discussions of this in the large group tend to center around angels — not unlike discussions of angels dancing on the head of a pin. We'll bypass them for today although we don't in any way minimize their importance because I think it's important for the Committee to be clear.

Also, secondary issues that depend, I think, on the fundamental algorithmic approach to looking at recommendations — we're also not going to discuss. One might conceivably want to formulate recommendations to minimize visits, and that could be done in the context of the timing intervals and so forth. That gets very complex and I don't think we're there yet in terms of being able to offer you anything on that. The other thing is unless there's only one algorithm in the world, and it's blessed and thought to be the standard, ultimately the question of validation of other algorithms is going to come up. That's an area also of added complexity.

So the first thing we're going to do this morning is to — we have core variables listed. I think the items in your package that are — that we're going to address this morning are the ones numbered two and five of the briefing areas. Specifically, they are the tentative core parameters proposal. In your hand-out, it's constituted as a list. How we'll present it this morning, however, is as a table. We've been working on making intuitive for everybody — not just for programmers. So I think probably paying attention to what Larry Blumen will present right now, I think, will be probably more informative than your hand-out.

Finally, I want to touch on after that, some of the issues related to later; we're doing immunizations. We've had discussions with Dr. Guerra, the Chairman of the work group, and others in the work group who I think have some comments — additional comments to offer over and above what we will present. So let me now — Mr. Chairman, turn it over to Larry Blumen, who will explain a schema, a proposed schema, for your review relating to computerization.

SPEAKER UNIDENTIFIED: John, I want to make sure which document — exactly which document we're talking about. Is it the algorithms document? Thank you.

KILBOURNE: Okay. Now I just want to explain that I think if you —it will be a source of confusion if you try to follow the hand-out at the same time as the table presentation. So probably, I think, making reference to what's going on up here is your best bet toward understanding. It is a little bit complicated, so I think I ask you to direct your attention to Larry. Okay, now Larry.

BLUMEN: What we want to present to you this morning is a work in progress. So we're not showing this with the idea of making decisions so much as stimulating discussion about an approach that's being taken. What we're doing is creating a method of abstracting from the existing official recommendations of the ACIP in text and tables as they exist — abstracting them into a more structured format that will be appropriate for automated algorithms to use as parametric input. We have an example

of this that we're showing on the screen now. It's organized as a table, and in fact, a set of tables because obviously, you can't get all the recommendations — all the variables that are implicit in the recommendations on one table. It would actually take a set of tables.

So what we're showing right now is one of the tables that you would need for the DTP, DTaP, TD series. I want to describe to you the basic dimensions; that is what this table represents in relation to other tables that would relate to the same series. This table, again, is for the DTP series, but it relates to certain vaccines that contribute toward that series, specifically, DTP, DTaP and DT pediatric. There are a set of variables that we'll look at in a minute that are pertinent to these vaccines. There is another table, for example, that we could show that would also have parameters for the DTP series, but would relate to the TD adult vaccine. Obviously, there are differences in the age parameters, as well as the intervals there. So you have to break these parameters up within a series according to the types of vaccines that are involved.

In addition, there's another dimension in which we have to break the tables out, and that is essentially in terms of the schedules that ACIP recommends for on-time delivery of vaccines as opposed to accelerated schedules. Those tables are "keyed," if you will to the age at which the child starts the series — when they got the first dose of DTP, for example. So in the ACIP recommendations, you have your own tables for the regular on-time schedule, and then you have another table for the accelerated schedule. The accelerated schedule picks up if a child receives his first dose of DTP at four months or later. Okay.

The computer then would have to make that decision by determining what the age of the child was at the time the first dose was received, and then select the right table of parameters to use on that basis. Okay. We're going to go back to the first table, then to describe to you the variables that we have selected for representation here. If you look at the bottom half of the screen, there are a set of columns that contain the parameters that would apply to all of the recommendations that ACIP makes. They are essentially parameters relating to age and interval. Within age and interval, you have recommended parameters and minimum parameters. That is, when is it customary to give the vaccine as opposed to what is the earliest date that the vaccine can be administered. Also, the minimum is also used in algorithms to decide whether or not a dose that's been given in the past is actually valid to count as a dose in the series. As if a child got two DTPs spaced a week apart, the second one would not be considered valid because it would not — there would not be sufficient spacing to get past the minimum interval parameter, if you will.

So the table is organized by dose numbers. So these are dose-specific parameters. The first column is the recommended age to give a

particular dose. That's the one that's probably the most straightforward. It's the one that gets on the little picture of the schedule that gets very wide distribution. There's not much problem in finding those numbers in the ACIP. So for DTaP, you have the two months, four months, six months, fifteen months and four years. Those are the recommended times for giving those doses. If you will, pardon me for preaching to you about the ACIP recommendations. That feels a little strange, but I am just telling you how this table came to be.

To the right of each of the parameters that we've listed, we have a number in parenthesis which refers to a series of notes where we're referencing where we have found the justification for the parameter in the ACIP. We feel that it's very important for this table to be grounded in the existing recommendations, and that we are looking for a valid basis for all of the parameters that we're putting in this table. These tables do come with a page of notes that will reference the ACIP text and tables.

The next column is minimum age to give a particular dose. This is an area where — the minimums is an area where we do find some gaps in the recommendations although there are not that many really, but as I say, this is important because it not only tells the computer how long to wait to provide the next dose if the child is already above the minimum age or — well, is the minimum age — but it also decides or helps the computer to decide whether or not to count the dose at all. Okay. Some vaccines have a maximum age for use. Above the age, the computerized algorithm will not recommend that particular dose. In the case of DTaP, of course, the seventh birthday is the transitional point. From the seventh birthday on, the TD schedule will kick in.

Polio — oral polio is another example where it's not routinely given above eighteen years of age. So the same rule in the algorithm can enforce the polio maximum age, as well as the DTP maximum age simply by the change in the parameter. Okay. Then to the right of the minimum age, we have the interval parameters. We have recommended intervals and minimum intervals. In the case of DTP dose number one — that is the interval from dose number one to dose number two — it's actually given as a range in the ACIP from four to eight weeks. So we took the lower number as minimum interval to follow and the higher number as a recommended interval.

In general, the algorithms would impose two tests to decide whether or not a particular vaccine dose could be administered. You have to pass the age test. You have to be above the minimum age, and in most cases, it'll be looking for a child to be above the recommended age. Then if that's satisfied, then you also have to pass the interval test. That is enough time needs to pass since the previous dose before the computer would recommend it. Okay. That's what those two columns are for.

The last column may need a little bit of explanation. We generally refer to it as the “skip age” parameter. In fact, it’s there primarily to deal with the rule that you have with the fourth dose of — the fifth dose following the fourth dose of DTP. Whereas, as if the child receives the fourth dose of DTaP on or after the fourth birthday, you get to skip the fifth dose. So what the computer would do with the parameter that’s put in there is that if it sees a parameter for the skip age, then it will determine how old the child was at the time that dose was received. If the child was older than the skip age, then it skips the next dose. If he’s younger, then it will recommend it. That’s what that is for.

One of the interesting things that have come up through this process is that we find that there are some cells within this table for which we can’t find an explicit recommendation in the ACIP text and tables. There are not that many of them, frankly. The recommendations are very complete in most respects, but they are there and this is the sort of thing that gives the developers of algorithms some problem in trying to decide what to do. The computer needs to have some parameter in each one of the cells in order to function. Some of the gaps that we found — first of all, this is our perusal of the recommendations. If anyone in the room can show us a reference to a recommendation that we’ve missed, we’ll gladly take the shading off some of these cells. The gaps are indicated by the shading in a few cells on the table.

For example, in the column for minimum age to give this dose, it’s clearly stated that dose one of the DTP series should not be given below six weeks of age; that’s there. For the second dose, there’s no interval that we can find that says “what is the minimum interval after the first one before you can get the second one?” So we’ve interpolated that figure from the minimum interval between the first and second dose, which it is in the recommendations, and that’s four weeks. Okay.

So if you can’t get the first dose before six weeks and then you have to wait at least four weeks for the second one, then that implies an interval of ten weeks, but that’s not explicitly stated in the recommendations. That might not be considered a serious omission, but it is there. As I say, it does present problems to algorithm developers. We are endeavoring to note the gaps throughout the recommendations as we encounter them in the hope that we can stimulate some discussion here in this group as to what, if anything should appear in those cells based on your deliberations.

The overall thing here is that we’re trying to create a structured format within which to present the existing recommendations of ACIP to facilitate the process of automating the recommendations by computer developers. I can tell you that if a set of tables like this were to be developed and

blessed by the ACIP, it would be received by systems developers very warmly indeed. It would make their lives a lot easier. We would get better algorithms that were more accurate, and they would have the official validation coming from this body. We will, over time, be doing this same sort of process for all of the series. We'll be presenting them to you for your consideration at a later time. Thank you.

McHUGH: I'd like to ask a question on the last table.

MODLIN: Quickly.

McHUGH: I just wanted to ask a question.

MODLIN: Again, please identify yourself.

McHUGH: Yvonne McHugh, Chiron Vaccines. Where you have doses in series unlimited, is that because you have a TD up there?

BLUMEN: That's correct. The number of doses in the series really applies to the whole series and not to any particular set of vaccine. So it might look a little funny on this table to see unlimited in relation to just DTP and DTaP where, you know, you've only got five of those. The TD adult is part of the series, and in that sense, there is no limit on the number of doses there since the TD — yes; it's represented on another table that's also part of this series. The computer — again, I keep referencing the computer — it needs to know how many doses are in the series so that when it examines an immunization schedule, it'll know whether it's complete or not or whether it needs to evaluate the schedule for the next dose.

MODLIN: Thank you.

KILBOURNE: The outstanding part of this table from my point of view — I hope it was clear — these are identifying data for the tables. Because of the different ages of the vaccines, you may — and the different times that they might be started, you have to have several different tables to completely cover the waterfront in summary. The outstanding things here are the fact that we don't have absolutely explicit minimum ages. They are inferred here based on the minimum interval the minimum age at which you could give the first dose. If you've got six weeks plus four weeks makes ten weeks, plus four weeks, you could be giving DTP-3 at fourteen weeks or three months.

As a parent, that struck me as odd. I'm reassured by Walt Orenstein that's legal and biologically feasible, but if unintended, having had the discipline of making this table would've made that apparent at the time of developing the recommendation. So that I think that if you — although

computer programmer developers have to concentrate on the extremes and look at sort of not the mainstream part of the recommendation, but maybe its unintended consequences at the extremes of the recommendation, it's still a valuable thing, I think, to do.

Can you put the second table on the — the childhood, the doses for childhood are very closely spaced and well parameterized, we would say, even though what you have are textual recommendations. When you're looking at TD in adults, what you find principally are ten-year intervals in between — not a lot of information on minimum interval or other parameters. I think here what you're dealing with is not necessarily having thought or not thought through the consequences of minimum intervals plus early ages of giving vaccine. What you have is — I believe what you intend is a fair amount of discretion or a certain amount of flexibility by not having these rigidly specified in the same way the childhood immunization schedule is.

In general, we found the parameters to be "findable." In other words, it's not totally a lost cause to try to go through the recommendations. The recommendations are generally well constructed and certainly fit the mainstream case very well. Some effort is required to find some parameters, and in some cases, we don't find them there; they're absent and need to be inferred. The question that we have is when we infer a number into a table, is that inference warranted? Is the inference intended or is it, in fact, intended to be blank and to allow for clinical judgment? So these are the questions with regard to absent parameters. Are they oversights? Are they purposely ambiguous? If one would specifically distinguish those on a table, that would probably be helpful.

We keep coming back to the role of clinical judgment and some way to deal with this. An MMR at eleven months and two weeks is probably not a tragedy. However, it's outside the bounds of what you all recommend. If social circumstances warranted it or there might be other compelling individual circumstances, we have heard in our discussions with the work group members that we would want to be able to invoke some flexibility and not just totally numerically try to run the immunization schedule. If there is going to be clinical judgment though, one would have to indicate it in some way. At a minimum, jumping to the third bullet, you would have to put down the practitioner's overriding the schedule such that this dose ought to be counted.

The override variable then becomes a new database element. It's not something that you can predict next doses on unless you say, "Yes, I'm going to take this into account" or else you will get the computer requesting every subsequent visit for that dose to be repeated and that's not helpful. Then also you run into the question — and it's really a question that immunization registries brings up. The immunization

registry, if children go from provider to provider — yes, they have their immunization records go with them — but also, do the judgments of previous providers follow them along? That situation, of course, already obtains without computerized efforts and individual clinicians make decisions to accept or not accept previous vaccinations, but maybe without as much thought as we're giving it right now.

Another alternative is the second bullet and that would be to — in addition to intervals and recommended ages, just to give a barely acceptable range where you might see the clinical judgment might wander a little bit, again, on the example, the MMR given a couple of weeks early, certainly given at six months, I don't think anybody here would say that that constitutes a definitive MMR-1 immunization. So that would be an alternative approach. It's complex, and I think subject to argument and not easily implemented. Just to touch on the question of late or overdue — one would have to, approaching this conceptually, one has to find what one is thinking about. We haven't done that yet, but just to review that thinking with you, if one were operating at a totally programmatic mode, one might say, "Well, a dose is overdue if it's over one month or two months overdue. Then, we will recall the patient at that time" because recall — the whole reason for doing this, remember, is immunization registries allowing and enabling a recall function. There has to be a time at which a parent is going to be recalled or a provider will be recalled regarding a missed immunization.

However, it makes sense to think that the time to "dueness," or "lateness" or "overdueness" might vary according the vaccine series. It might even vary according to the specific or particular dose within a series. Finally, it might vary, I think, even to a given clinical situation is the need for pneumococcal immunization — the same or same urgency in a patient with sickle cell disease versus a patient that's over 65 years old, but has no other predisposing factors. That brings you, I think, to the concept that there are really two reasons to think about lateness: one is biological importance; the other is running an immunization program and the need to ultimately get everybody immunized.

An example of a very biologically-based decision that might be made to call a dose late is in the case of a newborn infant of a hepatitis B surface antigen-positive mother where it might be a question of hours; that being beyond a certain number of hours clearly could biologically be called late. On the other hand, if you are looking at the third dose of polio virus vaccine in a U.S. infant who's not going overseas, and there's no other risk and essentially a polio-free environment, is that really a question for lateness in terms of a biological reason, or isn't that a programmatic reason? Isn't it — are you calling people late at some point simply to get them in the clinic so you can complete their series? So I think those are the two things.

What are — what can you do about that? I think you have three options. You can leave lateness or overdueness to the discretion of practitioners or programs and simply not deal with it. You could deal with some situations as late or overdue based on the biological characteristics of the disease, the pathophysiology and other aspects of the clinical situation. An extreme — the other extreme would be to go and to attempt to define lateness for all diseases and immunizations for which you make recommendations. In any event, unless you choose not to deal with it, lateness becomes another core variable and would be added to the table that we presented earlier. That's all we intend to present to you right now. I wouldn't be surprised if there's some questions on the table. We'd be delighted to answer anything you have.

MODLIN: We'll get to questions. Fernando, you're the Chair of the work group. Do you have anything in addition to bring up?

GUERRA: No, other than to commend both Larry and Ed for taking a very discussion or series of discussions and field that is evolving in many different ways, and to putting it into a way that, I think, makes good sense and that one can follow easily. I would just add to that that timing is very important for us to really try to develop some basic terms of reference and guidelines for the practitioners for the health departments that are in the process right now in developing these systems because there are a lot of very important commercial type of endeavors that are certainly informing this in ways that maybe are not always in the best interest of what is an efficient public health system. So I think that if we can, you know, develop a consensus around some of these concepts that Larry and Ed are presenting to us, it will certainly be very helpful.

MODLIN: Rich:

CLOVER: Although this issue may appear to be tangential to our charge, I think it has extreme relevance. In the last two or three years, there's been a growth of electronic medical record systems that are out there. The cost of these systems — largely due to hardware costs — have dropped significantly that a lot of practitioners are now buying these systems. Many of these systems have some level of decision support tools in them as it relates to preventive health guidelines. As many primary care providers are being required to see more patients in their settings, we're delegating to our nurses and our other staff the implementation of the preventive health services. They frequently will look at these computer-generated recommendations and just simply follow them. However, these recommendations vary across the board.

If you look at the complexity of some of our recommendations, you know — let me just give you a few examples: a child that presents with only one series of routine immunizations that presents at eleven months, two

weeks of age would get a different set of vaccines than if that child presented at one year and one week of age. If you look at — a parameter that was not mentioned was gestational age. If you reflect back on our discussions yesterday on rotavirus, that child that was born at 36 weeks of age, when that child is two months would get a different series of vaccines than if that child was born at 38 weeks of age. We've been vague appropriately because of lack of data in our recommendations, but if you look at how to write these algorithms, it becomes a little more important.

LE: I also applaud this effort. At Kaiser with our HMO, we're trying to do exactly the same thing. One of the difficulties is trying to match some of the different vaccines, for example, the *Haemophilus influenzae* vaccine. Some providers use the one with the OMP and the other one uses the HibTITER, which is a little bit throwing off. So that's some hurdles. The main point I'd like to ask you is whether you would share this with some of the institutions that audit managed care, such as HEDIS and so on? They do have some guidelines of what immunization rates are acceptable for good managed care. It would be very important that they follow the same criteria as you do in terms of when the child falls in and out of compliance.

KILBOURNE: Two things — if we developed and if it were development with government money, we would distribute this free — the code to anybody who would want to use it. One problem though with the HEDIS criteria that's not embodied in any of this is the — I think the current iteration of HEDIS says you don't have to have — be up-to-date on your immunizations unless you bid them with a particular plan for twelve months. They give the plan that much time to come to grips with it. For us, I think, we would look at this more clinically and that the child is either up-to-date or not up-to-date. In terms of evaluating a child as to whether their up-to-date, probably to the extent that we could accommodate HEDIS, I think that would be good. I would certainly make it more attractive to managed care folks.

MODLIN: Thank you. Dixie?

SNIDER: Couple of comments and a question, Ed. One is, I think the table approach is very interesting. I just wanted to remind folks that the Society of Medical Decision-Making — the *Journal of Medical Decision-Making* — has analyzed two of this Committee's statements. I know one was hepatitis B; I can't remember the other one, but they've done it with a broader approach. They looked at whether we have included everything in our statement and addressed all the issues. So it just brings to mind that this concept could be broadened in terms of looking at our statements prior to our releasing them, and make sure that we have covered everything that we want to cover. If we're leaving something out, we're not intentionally leaving it out.

The other thing more specific to your table though, it seems to me that in thinking about the rotavirus, for example, recommendations, that we would want to do this before we finalize the recommendations and again see if, you know, if we have all the information in there at least from the standpoint of what's needed for computerized systems to keep up with the, you know, with the visits. So that's something we might want to consider. The question is I believe you were talking about routine immunizations or developing them for those now, but it's not clear whether for high risk individuals who would qualify for certain vaccines, you know, under special circumstances but not be routine; whether that would be incorporated in this system ultimately or whether that, you know, that falls by the way side.

KILBOURNE: The special clinical circumstances obviously are a problem because if you have significant deviations from what you ordinarily recommend, the question is whether it's worth a whole other table or whether you incorporate those findings in a footnote. I think it just depends on how different you're going to make things. It sounds like with the premature infants and rotavirus, there might be enough of an issue that that would generate another table that would have a second immunization schedule be based on that.

I think that in terms of rotavirus, the rotavirus people who are developing the statement have been very kind and have shared that with us. We've reviewed that in a preliminary way, but I thought it was unfair to put up our findings without having — we've not even them back to that group. So I just didn't want to do that, but I think the suggestion is well taken and we intend to keep pursuing that. The final thing I'll just point out in terms of the structure that is increasingly being applied to policy and so forth, when structured abstracts first came out, I found that onerous. I was used to writing any darn thing I pleased. At the beginning of the paper, I felt that that unnecessarily restricted me. Now as I'm more used to it, I like it; I like knowing what to look for, where to find it and so forth. I think at the very least this way of going about it makes one think about perhaps even about situations that wouldn't ordinarily come to mind. That's one of the benefits of it.

MODLIN: One or two more comments and then we have to bring this to closure? Rick?

ZIMMERMAN: A couple of comments — first, a request if we could get copies of those articles in the Society of Medical Decision-Making. I think this has implications for the policies and procedures of the working group as well. I mean, should a table like this be part of ACIP statements or is this going to be relegated to another working group that has to keep meeting? So I think that raises a policy issue. In addition to the ones mentioned thus far — prematurity or gestational age — there's also issues like

influenza first dose needing to in certain age children, and a couple of things like that that hepatitis B and the surface antigen-positive mothers where you are going to end up with different tables. So there's a number of biologic issues that are going to change.

MODLIN: Thanks. Larry, last one.

PICKERING: Yeah. I think we've talked about this, but I think nationwide algorithms are available as part of the COSA Program to track kids when they're due for their immunizations. I think they're working very well. I think they're under Ed's or Larry's purview, and so some background data and experience are available in this area. What I want to do, I think there are four things as far as making this practical that we discussed and I think need to be considered. Number one is the operational issues that these programs need to have, of course, as much data inherent to the program as possible so that things don't need to be entered in excess. That needs to be very clear what needs to be entered. I know this is one area that's important.

Secondly is something that Dr. Clover mentioned and that is the rigidity with which these programs sometimes adhere. If the rigidity is such that it's not user friendly, it's going to be a problem. For instance, if a child has a cut-off of 28 days as a minimum interval between immunizations, then a child gets it at 27, you can't have this type of a program kick that out and not count that dose. So there has to be some aspect built into this so that rigidity doesn't make it so un-user friendly that it is not utilized.

The third area is the validation — the scientific validation, of course, which can be done, but also the physician or health care professional who's going to be utilizing this program needs to have a great deal of input. I know we talked about this and this plans to be done. Then lastly, the fourth point is there needs to be the ability to make immediate changes. When a change to the immunization schedule occurs and is accepted by all in the harmonized schedule, this program has to have the flexibility to be able to be changed immediately rather than six months down the road or you really defeat the purposes. I would also like to congratulate Larry and Ed on moving this important issue forward.

MODLIN: Likewise. Dr. Kilbourne, Dr. Blumen, thanks very much. We do need to move on. The next item on the agenda is the report of the Work Group on Combination Vaccine Recommendations. Mimi, I don't know whether you or Bruce Weniger will be introducing it. Bruce.

WENIGER: I've brought this summary of the working group's deliberations. Our Chair, Mimi Glode, will provide input as needed as we try to summarize where we have gone and where we are going. Let me just point out an area in your agenda for the meeting; that we're not asking the ACIP to

make a final decision today on this issue. Let me just summarize the timeline of where we've been on this. This is now the fourth — I think we can leave the house lights on if it's okay or maybe just dim them partly would be a little easier. I think you can see all of these slides.

This is now the fourth presentation before the ACIP starting last February. After hearing the recapitulation yesterday of the rotavirus experience, that doesn't make me feel so bad. Some people were consoling me that this was taking a long time after our last session in October. Since October, we've had two conference calls and three drafts have appeared. The draft you have in front of you has not yet been really fully reviewed by the working group, so it's still likely to change to some extent. We did meet yesterday for a brief lunch meeting. We did not have time to go into it in any detail except to discuss some major issues and a few minor ones. So we're asking the working group, as well as the entire ACIP, to provide us written comments on this current draft by the end of this month so that we can prepare another one and we'll also get these drafts into the other organizations harmonizing on this AAP and AFP for their formal consideration. As a result of those, we expect there will be further drafts with additional changes are coming in.

Let me say that the previous presentations before the ACIP, I think, have been very helpful in giving us feedback. A lot of written feedback came in from ACIP members not on the working group formally that has been very helpful. We appreciate that. So we expect to have one or more conference calls between now and the end of the spring. Our goal will be to try to have something ready for a formal vote next June — in July as they sometimes say.

In terms of where our progress has been and where we're going, as you recall from the last meeting, the issue of large vaccine purchasers was rather contentious, which has resulted from the pilot federal DTaP procurement policy. Let me just digress for a second to summarize that briefly. For 35 years, the federal government has had, *de facto*, a formulary of one brand of vaccine for every type; the state governments' health programs — immunization programs — ordered from that contract and there was no choice of brand. In 1994 with the onset of the Vaccines for Children Program, where federal vaccine purchase increased to what we estimate is roughly about 60 percent of vaccine doses for children in the United States, Congress authorized us to provide two — more than one contractor, basically waive federal procurement policy that you go with the lowest bidder. We ended up with a system in where the lowest bidder got roughly 60 percent guaranteed market share and the next highest bidder got 40 percent roughly.

In order to achieve those market sharing proportions, the states were not given the option to choose between two brands of the same vaccine.

They would have to order one brand. They would want 10,000 doses of DTP or they'd want 10,000 doses of Hib, and they would either get Brand A or Brand B at random and usually both in different shipments. Then their providers would also get two brands of the same vaccine, which had led to some confusion. With the anticipation that there would be multiple brands of DTaP vaccine, there are now three licensed, I guess, and more coming. A pilot project was begun last year where the states would be given the choice of brand because of the preference that you see in this statement and it's also in the pertussis statement that the same brand be used when feasible for the doses in the pertussis — in the acellular pertussis series.

So this was a very contentious issue as you recall from last time. It was decided — and there was no, clearly no consensus on the working group on how to deal with those issues. So it was decided to remove that issue from this document and basically allow CDC, if it needs to make policy or set guidelines, to use other mechanisms to do so than through the ACIP for the state health departments and others that participate with us in the National Immunization Programs. So that, I think, has cleared a large end to some extent and produced the progress where we are today.

We're continuing in these iterations of the drafts to refine redundancies and language to make it as elegant as possible. We're also searching for, you know, dealing with the ambiguities that I feel exist because our vaccine lexicon is not very precise in terms of the definitions or uses of words like "antigen" and "vaccine." You can ask how many antigens are there in DTaP vaccine; some might say three, but if it's the Connaught product, it's actually four because there are two pertussis antigens. How many vaccines — is DTaP three vaccines combined into one or is it one vaccine? So sometimes, it's difficult to use words precisely and to avoid ambiguities in that.

We're also working on trying to determine in a subject that is very cross-cutting, dealing with issues of science, practicality, public policy and even some politics. What are the limits of relevancy to the subject of combination vaccines because they raise all sorts of peripheral issues. There's some trade-off. Obviously, the more peripheral issues are — that some people consider peripheral; others more central that you put in the longer the document. So it's sort of the classic lumping versus splitting, or should we high gloss some of these topics and send them to some other working group, or put them out not to be addressed until some later date, or should we keep them in this document?

Examples might be interchangeability of monovalent vaccine. It's obviously a combination vaccine statement, but we also have a few sentences in there talking about — when we talk about interchangeability of the combinations, we'll mention a few interchangeability issues related

to monovalents as well; extra doses of adult vaccines, even though it's a childhood statement. That was suggested we cover at a previous ACIP meeting; I think it was June or February of last year. The improving of recordkeeping sytems since combination vaccines raise a lot of questions as they get more complicated — keeping track of what a child actually got; that will be more difficult, and of course, issues of supply, inventory and formulary. The word "formulary" does not exist any more in this statement. That's obviously a red flag type of word.

Finally, we've been dealing with the issue of how to harmonize with this because it wasn't really into mid-stream in the process in October when it became clear the other organizations would be trying to harmonize with ACIP on this topic. The outstanding issues that I think — and it's outstanding in the sense that the major ones, as well as the ones that still need to be resolved to some extent, are how we handle this partial harmonization. If you look at the footnote on page three of the document that you all have, it's a somewhat novel approach in which the other organizations would subscribe only and publish only the identical boldfaced, indented major headings one through six, but not necessarily publish the same explanatory text and qualifications text.

To avoid any surprises, we've shared this concept with the MMWR just very recently and they will be thinking about it and considering it along with the senior policy levels at CDC before we can get a read-out. So I think the feedback — I think they're going to, informal feedback I got is that they're going to want to think long and hard about it. You can read those tea leaves as you will. The issue is surprisingly, only a few weeks ago, we have to admit discovering that the recently published harmonized schedule that came out last month, as well as the one that came out a year ago in January of 1997 had a sentence in the footnote that would — is inconsistent with the issue we've been dealing with on when it's proper and okay to give an extra antigen in a combination vaccine where the child needs only some but not all of the antigens.

I've shown the language here that would have to be either fixed or dropped from future schedules — it's been struck out here — "some combination vaccines are available and may be used whenever administration of all components of the vaccines is indicated." This is inconsistent with what we're proposing in this draft. The language that came out of our discussion yesterday would substitute for that — something to this effect — "some combination vaccines are available and may be used whenever any components of the combination are indicated and its other components are not contraindicated." We deal with those issues in detail in the text.

We also discovered that another mistake in the footnote — it's not relevant to combination vaccines, but I've just put it here in terms of the

dosing age range for the second dose of hepatitis B and HBSAg-positive mothers. So hopefully, some other group will look into fixing that. So I think in the remaining weeks and months, we'll be basically fine tuning the sections. I think the three sections that will probably get the most focus and attention are some of the most difficult ones — the interchangeability section, the section on extra doses of vaccine antigen and the strength of evidence table in the back. I think we also discussed, and I think will be very useful, these are difficult issues to express clearly. We often, I think, can understand what we mean, but we're not necessarily certain that a practitioner on the front lines in the clinic is going to understand — is going to interpret were we writing it the same way we intended it.

So I think it's going to be useful to try to get this draft; that whatever informal mechanisms we have into the hands of practicing pediatricians to say, "Does this make sense to you? What questions does it raise?" If they are consistent questions that keep cropping up, "Well, you said in this circumstance do this, but what about this somewhat different circumstance? What can or should I do?" If we can learn what that is, I think we can either address it by changing the language or perhaps to avoid the possibility of having to publish a frequently asked question, supplement in the future when we realized that there were ambiguities or other circumstances that we didn't address. So I think that that will be important to do.

Now I have the six boldfaced recommendations on three sheets here. I wonder if it would make sense to go through one sheet at a time while it's on the screen and open it up to discussion, rather than go through all six and then open it up to discussion? Is there any preference? Do them two at a time basically so we have them in front of us and then open them up to individual discussion?

MODLIN: Sure. I think we have the time. Why don't we do them two at a time? How about that?

WENIGER: Okay. Well, we'll start off — these are the same as in your draft, although I've made some of the corrections that we — a few of the corrections and changes that we discussed yesterday in our working group. The first one is basically, the preference for combination vaccines and when in general use them because they will save the child extra injections and avoid all the consequences that flow from that. The second one was the interchangeability one and this middle potential addition was deleted yesterday, and some wording changes were made here, but basically that you can use in general vaccines from different manufacturers against the same disease interchangeably except the major exception to that is the pertussis — acellular pertussis vaccine in which when feasible, you should try to stick with the same manufacturer. The exception to the exception is

that when you don't have it, you can use whatever brand you do to complete the series. So any comments or discussion on this?

MODLIN: No. Let's open it for — I think both of these points are obviously critical issues. Mimi, do you want to lead off?

GLODE: If you go back to the first one, Bruce, just to mention that I think both the ACIP, as well as the working group has — this looks like a simple sentence, but you know — has spent a moderate amount of time voting on things like "is strongly," "preferred," "is recommended" — is whatever. So I think you all need to read that carefully. "The use of combination vaccines is preferred over the separate injection of their equivalent component vaccines in order to minimize the number of injections a child receives." So again, we're hoping the six large boldfaced recommendations, at a minimum, that these six will be harmonized and relatively widely distributed. We want them to mean something, but we want them to say, you know, to have the strength that the recommendation be what the Committee feels is appropriate.

MODLIN: Neal? Larry?

HALSEY: Bruce has raised many issues. If you want us just to focus the discussion on these points. . .

MODLIN: On these points, yes.

HALSEY: . . .I would be happy to.

WENIGER: Well, we can go through these relatively quickly and open it up to the broader issues afterwards. Does that make sense?

HALSEY: Yeah. I think. . .
MODLIN: Okay.

HALSEY: . . .as I reread the second one with the changes that were made at the discussion yesterday, I think the wording is cumbersome in the second sentence of the second one. It really can be made simpler; it should be made simpler and I think we can do that, but the concept is there.

WENIGER: Sure. Well, I think the most convenient thing is to get these suggestions in by phone call or in writing especially so that they can, you know, they can put into the next draft.

MODLIN: Maybe it would be a good idea to go through the other four, Bruce.

WENIGER: Okay. Alright.

MODLIN: And then we'll open it up.

WENIGER: Okay. Then we'll open it up in broad discussion. The third one was the issue of vaccine supply. This is obviously the one that's gone through a lot of careful thought, and discussion and debate. "Immunization clinics and providers should maintain a supply of vaccines that will protect children from all the diseases specified." Basically, the clear intent is that everyone should stock whatever vaccines it takes to prevent all the recommended vaccine preventable diseases; that would include varicella and the others that some practitioners are not using, hepatitis B and so forth.

The second sentence — "this responsibility may be fulfilled by stocking a variety of combination and monovalent vaccines." This was changed. Some suggestions were made yesterday and I've tried to indicate them here. I'm not sure if the strike-out is showing so clearly in the back. ". . .by stocking a variety of combination and monovalent vaccines. However, they may choose not to stock all such vaccines available, nor multiple brands of each." So a few minor changes were made to what was sent and there's certainly the possibility that we can discover more elegant language than this.

The key issue, of course, is do they have to stock both a DTaP-Hib and a Hib-HepB? The answer is, no, you don't. Do you have to stock multiple brands of DTaP because of the preference to use the same brand for a child who might've been vaccinated elsewhere? The answer is, no, you don't. So I think this is an area where showing that the practicing pediatricians and family practitioners who can say, "Well, what does this really mean?" If they have — if this doesn't answer all their, if this raises more questions, we need to fix the language so that we can avoid the need to supplement this later with frequently asked questions because a lot of the burden we face in NIP is the phone calls of those frequently asked questions. So the more we can resolve them here, the easier life is day-to-day.

The next section was the extra doses of vaccine antigens. "The use of a combination vaccine containing some antigens not indicated at that time for the patient may be justified when products which contain only the needed antigens are not readily available or would result in extra injections, and the benefits to the child outweigh the risk of adverse events, if any, that might result. A few extra doses of most live virus vaccines and of Hib and HepB vaccines have not been found deleterious for most patients. Extra doses of certain antigens, however, such as tetanus toxoid and pneumococcal polysaccharide, may increase the risk of hypersensitivity and related reactions." We put in here some examples of when it's okay and when it's not okay just to make it clear that there

are cases, and hopefully, they will look at the fine print to read more about those.

Moving on to the last two boldfaced sections — one of them is the recommendation. Here's where Neal came up with some helpful suggestions yesterday to reduce the verbosity of this one. I'm not sure — I'll read it because it's a little hard to see the strike-out. "Immunization programs should give high priority to improving systems for (a) transferring vaccine identifying information into medical records and immunization registries, (b) reminding patients/guardians to obtain needed vaccinations, and (c) informing providers of the prior immunization history of their patients." I hope that I caught your suggestions yesterday, but we can fine tune this. I think you'll be hearing later this morning about this — some initiative to try to begin addressing these. I personally feel it would helpful to have some language from ACIP supporting the initiative you'll hear about later this morning.

Then finally, on research priorities, basically a laundry list as in any other statements of what future research needs to be done — "further efforts are needed for studying interchangeability between vaccines, the safety efficacy of administering combination vaccines for patients who already are up-to-date on some of the component antigens, economic and operations research on the selection of vaccine inventories, and research to develop and evaluate alternative means of vaccine delivery that would avoid the problem that combination vaccines are trying to address," which is the increasing number of antigens we have to squeeze into a limited time frame, and a limited space on the child's arm and the limited tolerance of the parents and the doctors to give so many shots. So I think that is a brief summary, and now we have a reasonable amount of time for discussion on the broad issues and any of these particular ones.

MODLIN: Thanks. Rich?

CLOVER: It's probably very appropriate that this discussion is occurring after the algorithm discussion because looking at this, you just added another level of complexity to the algorithm discussion because now you've taken it down to the brand name if you're encouraging, for instance, the same brand of DTaP to be used. I would encourage the Combination Working Group to have the Algorithm Working Group look at this current vision to see if these phrases can be incorporated into their algorithms.

WENIGER: That's an interesting point. I guess from the computer programmers' perspective, if a child does not get the same brand, you cannot tell just from looking at the immunization record whether that change of brand was supported by this document because the document just didn't have it. Will the computer program determine the child is not properly immunized? So that's a policy question, I think. It would seem to me,

having worked on this statement, that the child is properly immunized and we can't — I can't figure out a convenient way that you would get into the computer record the circumstances when a different acellular pertussis was used, but that's a good point.

MODLIN: Challenge for the programmers. Other comments on any of these points? Mimi.

GLODE: Now that I see it in large bold on the screen, Bruce, for number four, *Extra Doses of Vaccine Antigens*, I wonder what the Committee — I was a little worried about that last sentence that says "extra doses of certain antigens, however, such as tetanus toxoid and pneumococcal polysaccharide, may increase the risk of hypersensitivity and related reactions." I'm just wondering about the word "hypersensitivity" because what I'm aware of is an accentuated local reaction that's believed to be an Arthus phenomenon, at least with tetanus toxoid. So is "hypersensitivity" the right descriptive word or are we — might it be interpreted as we're going to cause anaphylaxis or something.

WENIGER: Yeah. I think we mentioned in the general text the word "Arthus." I think this was intended as sort of a substitute for the more technical term, but it's not meant to imply anaphylaxis. I think any suggestions for improving it would be helpful.

SNIDER: There's one term in *Immunology* that does imply IgE-mediated reactions.

BREIMAN: Reactogenicity.

WENIGER: Reactogenicity?

SNIDER: Right.

WENIGER: ". . .may increase the risk of reactogenicity" period, and leave it at that — something like that.

GLODE: Or local reactions? I mean, I'm not sure we want to imply a systemic reaction here.

BREIMAN: There is some question about whether or not that will occur when pneumococcal vaccine is given close together, you know, the possibility of anaphylactoid reactions. There have been several published reports. So it's not totally, you know, off-the-wall to suggest that, but I think the bigger concern is about, you know, local, you know, reactions.

WENIGER: I think this may be one of the reasons why there's some concern over emphasizing too much the boldface, and not enough the qualifications, and exceptions and detailed explanation in the general text.

FLEMING: I have a minor concern about that. I'm not aware of there being any combination vaccine for pneumococcal polysaccharide vaccine. I was just wondering whether we might want to choose an alternate example because reading this in that context could imply that there's a combination vaccine out there with pneumococcal polysaccharide.

WENIGER: We have been informed by industry that they are planning — although we don't know what stage of development; if we did, we may not be at liberty to say publicly — but they are planning pneumococcal vaccines in combination with others. Where they are in their planning stage, I cannot say. The other issue I raised earlier was that there are some — when the combination vaccines raise the issue of extra doses or of interchangeability, we have included some additional data on vaccines that are not technically combinations because they were related to the subject that we're discussing. This was suggested by ACIP members and others that, "Well, you should put in this comment. What about adult — what about extra doses of vaccine for pneumococcal, which is not currently a combination as we speak of it?" So this is a lumping versus splitting, okay. If we take out that example, what examples do we use to illustrate the concept that some extra doses are not permissible?

MODLIN: Thanks. Paul Glezen.

GLEZEN: Well, I think there's a very real possibility of carrier mediated suppression. I think that's what's going to have to be guarded against. A paper by Mulholland in *JMA* on active immunization where tetanus toxoid had been given followed by the conjugate vaccine. The conjugate advantage was lost by the prior immunization with tetanus toxoid. So I think that's something that's going to have to be guarded against in the use of various combinations because if you add up large amounts of tetanus toxoid by active immunization with tetanus toxoid plus that uses carrier protein, then you can lose the advantage.

WENIGER: We do comment on this at the suggestion of David Scheifele from the previous meeting in the document at the end of this section. The page number I can give you, but we do comment on the concept that there's a potential theoretical risk in the future if we continue to conjugate new vaccines with the same moiety protein, whether it's tetanus toxoid or whatever; that we'll be giving many additional doses of that toxoid and there may be some sensitivity as a result of that.

MODLIN: Rick.

ZIMMERMAN: We had some discussion in the working group yesterday about Section V, *Improving Immunization Records*. The question was asked — do we wish to keep this section as a number of the things, for instance, the registry and that type of information is being handled by the log algorithm group,

and reminder and recall statement which is fairly close to being published is also handling most of item B. So do we want to have this section or not? It might be useful for the working group to hear the opinion of the Committee members on that.

MODLIN: Do the others have an opinion about — specifically about the issue that Dr. Zimmerman raised in terms of keeping Section V in the statement?

GUERRA: There is a need for Section V, but there maybe doesn't have to be such an extensive section. Rather, it could cross-reference with particularly the algorithm.

MODLIN: Right. Well, after hearing both presentations this morning, I think it certainly might be very reasonable to ask the members of the Committee, and liaisons and others to reread this section with that comment in mind, and maybe make comments regarding that when we get comments back to Dr. Weniger by the end of the month. Would that be reasonable? Neal.

HALSEY: On number four, just to take care of the concerns that were raised — again, always trying to move towards simplicity rather than complexity — why don't we take that second sentence and say "extra doses of certain antigens, however, may increase the risk of adverse reactions," and get rid of the specific example and not, you know, quarrel what hypersensitivity means to different people. I would propose, I'd like to move to the general issues if we can. I think a key decision that the Committee needs to make today is whether or not there is a correction in the harmonized schedule, as the points that Bruce brought out or trying to resolve, and then I can give a brief statement as to where we stand from the Academy of Pediatrics with regard to this if you would like.

SNIDER: With regard to your first point, we might want to say "adverse consequences" to get in Paul's concept as well. We're talking about interference.

HALSEY: "Consequences" to me means doomsday. I mean, it's a little bit bigger. I just worry that it might be over-interpreting. I don't know; maybe we can find another word, but trying to simplify it is. . .

SNIDER: Okay.

MODLIN: I think the intent of the sentence too, Dixie, is to mention specifically that the risk of increased reactions, whatever they may be, so I would suggest we keep Neal's language.

SNIDER: So there's no intent to be worried at all about the point Paul raised?

MODLIN: Well, I think there is.

HALSEY: Paul is correct.
MODLIN: He's right.

HALSEY: There are additional studies validating Mulholland's observation that I'm aware of and that will be published shortly.

SNIDER: I would suggest some thought be given to trying to get that fixed. . .

MODLIN: Good point.

SNIDER: . . .in there, whatever language.

MODLIN: Chinh, go ahead, and then we'll come back and discuss the issue that Neal has raised.

LE: I guess another general comment is, you know, the title of this draft is *Combination Vaccines for Childhood Immunization*. There are several issues that certainly overlap with adult immunization, such as now we recommend the wider use of MMR in health care workers. Hopefully, in the next few years, we'll have DTaP for adults hopefully. I just wonder whether with very — some minor readjustment — whether this document could be *Combination Vaccines for Immunization*, so that we don't really have to reinvent the wheel or rehash this problem two or three years down the road.

WENIGER: I might just point out it started that way and somewhere along the way there, a suggestion came in — *Childhood Immunization* — to keep the focus limited, but either way is, you know, would be acceptable.

MODLIN: Let's go ahead and open up for discussion the question of the apparent conflict that we have now between this statement and the current ACIP recommendations regarding combination vaccines. Neal, you said that you wanted to begin with a statement regarding this.

HALSEY: Well, I think that — well, I can talk about the Academy and where we're at, but I think it's best to focus on the harmonized schedule, which, because we have all three Committee representatives here. I think it would be useful and we support the correction. It's my recollection that it really is an error in the statement that the word "all" got inserted. The word "all" is not in the 1997 or 1996. . .

WENIGER: I checked it last night, Neal. It's in the MMWR of January 1997. Now maybe it's not the *Pediatrics* of January 1997, but it is in the. . .

HALSEY: Well, we will actually make a phone call and try to check, but the intent — I mean, Georges Peter is the one who made the suggestion that the word "any" be used in a conference call. I thought that that's the word that was going to get in. Somehow, the word "all" got in and some people objected to the word "any." That's why the subsequent sentence has been written. So we support the second sentence. I think it also can be simplified. I don't think we need to say "some combination vaccines are available." I think we can just say "combination vaccines may be used," again, getting rid of unnecessary words. "Whenever any components of the combination are indicated and its other components are not contraindicated," I think that's a simpler way to state it. We're certainly in support of that.

The second footnote, I think, Bruce, in the discussion yesterday, it was pointed out that that's really for infants of mothers whose hepatitis B surface antigen status is indeterminant — not the ones who are known to be positive. There's an inconsistency with regard to the timing of the second dose for infants whose mothers are known to be surface antigen positive and those that are indeterminant. Hal Margolis presented to this Committee information a year or more ago when discussion of hepatitis B that we can give the second dose at one to two months of age. We really need to be consistent for the two situations. So that's also an oversight in missing it in the development of this. So I think we could correct both of them as an errata in the various publication sources if we were all in agreement.

ZIMMERMAN: It sounds fine from my perspective for AAFP.

WENIGER: Is this something that you would want to just put out and have ACIP vote on today — this correction — and then publish it at the next available. . .

HALSEY: It does raise an issue that was discussed at length here when we were going through the frequency with regard to revision of the harmonized schedule and there are problems. From the Academy's perspective, we're constantly sort of reprinting this on almost a monthly basis to be distributing. I really don't think making those changes is very difficult for us, but I understand from some of the states that it's more problematic; that at the beginning of the year, they may be printing a very large quantity that they would be using. So it's an issue more from the public perspective — public clinic perspective.

MODLIN: I'm not sure if this requires a vote if it means — or simply correcting an error in the harmonized schedule that is clearly an error and inconsistent with ACIP policy. John, do you have any feeling about that?

LIVENGOOD: No. The only — I certainly can submit this to the MMWR. It'll run as a short thing at the end of it, but the problem is most people will never see

it. I would think that most states have already printed up what they're sending out for the year. I like the idea; I mean, I agree with the language very strongly. I don't know how we got from "any" to "all" because I can recall the conversation at that point. So we can certainly put it in as an errata, but I think that we'll have a little bit of trouble necessarily getting it to all the other sources, but it just — then when next year's comes out, it will be served.

MODLIN: Dave Fleming, or Fernando or Barbara, does this have much of an impact on your operation at all? Okay. Good. Dr. Faggett?

FAGGETT: You have the — we've probably already addressed this, but I think as practicing pediatricians, you know, we do for as much freedom of choice, I know open and closed formularies is a real issue. My question is I need — probably need some clarification when you talked about number III, *Vaccine Supply*, where the — I'm not sure what the purpose of "they may choose not to stock all available vaccines types, nor multiple brands of each." My concern is that physicians being not — pediatricians being denied the availability of certain products which they're comfortable, clinically comfortable with. I'm not sure what the AAP and AAFP positions have been on that. You might've — is that still on the table or what's going on?

WENIGER: Well, I think you're rasing the whole issue that we tried to remove from this working group to avoid the differences of opinion and the lack of consensus of whether or not state health departments or major vaccine purchasers, HMOs would have to allow physicians cooperating with them with either private patients or vaccines for children patients to have a full range of choice of the vaccines that are going to be provided. That was the contentious issue that was removed from the document.

FAGGETT: That's probably wise. I know in Tennessee that it was very attractive for us as pediatricians to have a more open formulary type approach. So I think you're on the right track.

MODLIN: Thanks. Further comments? Neal?

HALSEY: I would only just take the opportunity. There is a concern that is being raised since the issue has come up again about states only purchasing from a — or getting their supply from a single manufacturer through the Vaccines For Children Program. This has been discussed at a couple of levels of the Academy of Pediatrics. There is concern that is being raised by pediatricians that they are being denied the opportunity to at least have a choice between two different products when there are three or four out there for the different products.

Just as a statement of policy, we haven't formulated this yet, but I can assure you that the Academy is in favor of at least allowing for some

choice in those situations and not having it mandated because of the Vaccines for Children Program that they really are forced to use a single product. It's also not in the best interest of both public health and the private providers to be excluding manufacturers from the marketplace. That's the direction that I see that moving. So I think we are strongly in favor of purchase from multiple suppliers in whatever situations that it's possible when there are vaccines that are considered to be equivalent. Administratively, that makes it more difficult for CDC, but that's certainly where we are.

FAGGETT: Okay. Neal, would you say that number III — "may choose not to stock all available" — does that deny? What does that mean?

HALSEY: I can live with that language because I think it just — the intent of this is that you don't have to have all four types. It doesn't restrict people to one type, so I think the language in here is okay, but it's a separate issue that needs to be dealt with separately and it is a very important issue because it's also happening with HMOs, insurance companies reimbursement and so forth. We're not in favor of moving toward single manufacturers providing all the vaccine as is occurring in Canada right now. That's a disaster for us.

MODLIN: Thanks, Neal. I think the message has been heard. Any other comments on the combined statement — combined vaccine statement? Marie?

GRIFFIN: I just want to — I mean, Neal, we've sort of been through this and we went back and forth, and people have very different opinions about it. So I don't know if you're trying to open that up again, but I think that's going to present Bruce with some real problems if that has to be revisited because I think everybody was sort of happy with not saying anything more about it.

HALSEY: In this statement, I agree with not saying anything more. I'm just, you know, stating the Academy's policy or — I'm sorry, the Academy's developing position.

MODLIN: Any other comments about the combined statement? This obviously represents a tremendous amount of work and effort on the part of Dr. Weniger, and Dr. Glode and the other members of the working group. I want to thank everyone for that. Tom?

VERNON: On footnote number one, it seems to me the issue of correcting the statement is different from the issue of how it's distributed, how it's disseminated. Is it not important for the Committee to accept the correction so that whatever mechanisms are necessary to disseminate the correction can then be put in place?

MODLIN: Certainly. Shall we take a vote on the correction?

SNIDER: Yes.

LIVENGOOD: We'll do it.

MODLIN: That was my sense; that the correction will happen. Those in favor of. . .

WENIGER: Shall I re-read the. . .

MODLIN: I'm sorry.

WENIGER: Shall I re-read the text as it's been edited on the screen here?

MODLIN: Yes, thank you.

WENIGER: I guess the motion, I guess, was stated as that second sentence would be replaced by "combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated." Now there may be some ways to make that better. Perhaps if we could have some flexibility to maintain the intent, but maybe massage the words a little bit, that would be helpful. I'm sure that can be said more elegantly.

LIVENGOOD: Let's not go for elegance.

WENIGER: Okay.

MODLIN: The motion is made — has been made and seconded that the Committee accepts the change as outlined by Dr. Weniger. Those in favor? It's a unanimous vote for the nine members that are present. Thank you. Again, to finish up, I want to thank everyone for their efforts so far. We will try to vote on a final draft — a final draft of the statement at the June meeting. I would urge everyone to get their comments back to Dr. Weniger by. . .

LIVENGOOD: The end of the month.

MODLIN: . . .the end of the month. John?

LIVENGOOD: We wanted to talk a little bit about the harmonization issue, I thought, between AP, AFP.

MODLIN: Okay.

LIVENGOOD: Because I think the progress that we've made is opening the door to complete harmonization rather than just the partial harmonization that this version was sort of assuming would happen. I think that that is an

important enough development that we ought to try to see if we can work that out. So I think that's what Neal and Rick wanted to talk about.

MODLIN: Rick?

ZIMMERMAN: AAFP has commissioned that and is favor of the boldfaced wording because of the length of the document that we reviewed in January. Because of where AAP was at, we were just voting and looking at the bold thing. I think we're willing to reconsider the issue, but what it brings up is we need to go back to our Commission with the full document instead of just the boldface, and it means that our committee will have to read line by line all of the text instead of just the bold. I think we're willing to consider that, but we did not read it and vote to pass the entire document. We're willing to relook at it. Our next meeting is in May, so it will be before the meeting. There will undoubtedly be comments. If we look at every line of the text, we will have comments. I mean, that's going to happen.

MODLIN: I assume that there will be opportunities for the working group that will continue to work on this between now and the next meeting, including the time after the meeting of your group. So I don't — this should happen. Neal?

HALSEY: Yeah. At our October meeting, the Red Book Committee voted to basically try to come to harmonization on the boldfaced text, but we had rejected most of what was in the text at the statement at that time. That was in October; it's two drafts ago. I think in the last conference call, we made considerable progress at getting rid of unnecessary text and redundant information, and things that made it lengthy. I still think there's a fair distance to go to having a statement that will be useful to practitioners and I think, but it may be possible and we would be more than happy to open the door to trying to have harmonized text, which certainly is an appropriate goal.

SNIDER: I certainly would appreciate it because it fits putting out something in which we say other organizations agree with part of this, but not necessarily other parts.

HALSEY: Not really in the sense that we are issuing a separate rotavirus statement. We have separate statements on measles, and mumps, and rubella vaccines and acellular pertussis where we basically have the same principles and recommendations, but we clearly have very different text.

SNIDER: No. I was just talking about my problem with the MMWR footnote.

HALSEY: Yeah. Well, it's an issue of whether you put the Academy's name on the MMWR article or not is what it amounts to.

SNIDER: Yes.

HALSEY: Well, let's just see if we can come to complete harmonization.

WENIGER: If that were to occur, then what difference would the title page of this draft compared to other fully harmonized statements? Is it that the AAP and AAFP names are not mentioned on the title page? So I guess that's an issue that we'd have to address. If it were being fully harmonized, then it would say recommended by the three bodies on the front.

MODLIN: Further discussion? Thank you. Let's move on then to the next item on the agenda, which is an update — informational update on the policies and procedures. It's not really a statement as Dixie pointed out to me, but this is CDC policy that obviously, intimately involves the ACIP. I'll let Dixie lead the discussion.

SNIDER: Thank you, John. Just for those who have not been on the Committee or been at these meetings, I guess over the past 1½, actually two years, we've been developing these policies and procedures. There were several things that caused us to develop the document, which is in your notebooks. I don't think I need to recount all of them. I have alluded to some criticism of ACIP statements in the medical literature. I didn't allude to all of them, but some of those criticisms were — well, clearly there have been a lot of criticisms of ACIP statements, but some of those have been criticisms of the methodology.

There has also been — there were a number of things raised, I think, especially during the discussions of the polio statement that caused us to consider not only the methods we use, but to make — to put them down on paper and make it clear to folks what methodology we were using to develop statements. Another input into this was the development of a CDC document called *CDC Guidelines, Improving the Quality*, in which a group of people who are especially interested in evidence-based medicine decision analysis, cost effectiveness analysis and so forth, got together and wrote for CDC their ideas about how guidelines, recommendations — whatever you want to call them — should be developed. So that clearly impacts in this Committee because it was directed toward all the advisory committees of CDC.

So as a result of that and a number of discussions within the Committee meetings themselves about various issues, a working group was formed that was chaired by our then Chair Jeff Davis. A number of people served on it — some of whom are still here with us; others who have rotated off the Committee or rotated off as liaison members. In any event, I think it's fair to say that the initial document and still the basic issues in the document are issues that were often hotly debated by the working group. This document has been brought before this group — not

necessarily with these members — but this group on at least two occasions for discussion. I have made some presentations around some of the most controversial issues and gotten feedback.

Most importantly, we've gotten, initially, a lot of written feedback from the members, the ex officios, the liaisons, and we did all that we could to incorporate those suggestions unless they were 180 degrees apart, in which case it becomes a controversy that needs to be discussed and resolved. In addition, however, there are a number of other people who have reviewed this and had their input. We do have Committee management here, as well as our Committee management specialists. Gloria Kovach who needed to look at it from her perspective and from the regulations that govern the federal advisory committees; the Office of General Counsel felt that it was important to add certain sections in there, especially for new members, but also for others who might need to be reminded of certain issues, particularly those surrounding conflicts of interest.

I think it's fair to say that the document — the earlier documents were perhaps more ambitious in terms of what was being requested of the Committee and the programs. We have asked the programs to look at this document very thoroughly. On the one hand, wanting to produce recommendations that would stand any test of scientific credibility of them; on the other hand, recognizing that we have certain limitations and resources here at CDC — the staff already being considerably overworked. So we did a reality check with the programs. I think the programs did a reasonable job at responding back about what they could and couldn't really do. So we have modified the document with that in mind because we don't want to create false expectations on the part of the Committee.

I think they did this in good faith and I'd have all the programs, including the one that contributes most, NIP, recognized where we were trying to go. I think they have tried to retain as much of the changes with regard to doing things along the lines of evidence-based medicine that they could possibly could and felt that they could handle. So that's how we got to this point with this particular set of policies and procedures. As John mentioned, we actually could have written up ourselves the policies and procedures we wanted you to follow as our advisory committee, but that didn't seem to be a very wise approach since you might not buy into that or agree with that. So we're happy we took the approach that we did and had all those who have a stake in this to have an opportunity to comment on it.

I guess the last thing I'd just like to say about it is I don't view this as the end product that we live with, you know, for years or even months as the situation arises. I view this as a dynamic living document that we utilize,

but change as situations change. If we indeed, for example, want to add to this document for consideration at the next meeting or the meeting after, depending upon how much we have on the agenda, if we want to add something along the lines of the table I was talking about earlier, I think all of us would be receptive to talking about that, and discussing it and deciding if we want to put it in the policies and procedures.

I guess at this point in time, what I would like to recommend to the Committee — unless there's something really fatally flawed in the policies and procedures — is that we go ahead and adopt and follow these policies and procedures anticipating, you know, we will do that for the next meeting, and then continue to modify the document over time as needed. So I guess my central question is are there things in here that people find objectionable to follow at this particular point in time? People would be very concerned about our adopting some policies and procedures. I would point out at this point — particular point in time — we have no particular policies and procedures. So this will be a step forward to just have something that we can show the people who ask whether that's Congress or any interested constituent of what it is we do.

MODLIN: Or how about any other suggestions or comments — not just those that people can't live with? Chinh.

LE: Yeah. I read through the document and I find it is very, very useful. I really don't have major objections. I think that the point I want to bring up to discussion is your emphasis that, yes, the document is there, but we should really follow it. Let me take an example. Maybe with a new chairman, I think things will work, you know — let's maybe have a little brainstorming session regarding that. I think, for example, my experience looking back at the vote on rotavirus and how schizophrenic I was about it. The question is we were presented with a tremendous amount of data, especially the cost analysis data, you know — very well done, but it was rapid slides or transparencies. No "new data" was presented during the interval in the last six months or whatever; absolutely no new data was very clearly emphasized. We went on with that new data to make a vote that we refused to make a vote for anyway.

During that time, it would've been so helpful for us to be able to review, you know, two or three weeks in advance — again, the cost analysis data — because there were questions that Dr. Clover brought up, myself brought up that were not really well answered. Why did six months go on without a little bit more explanation to the Committee? Again, so you know, it states in here that "materials should be mailed fourteen days in advance prior to the meeting." Again, when we make such a big, big decision with tremendous economic impact, I would feel much more comfortable if we really had the raw data to look at ourselves and to share with our colleagues before we make major vote changes. Again, I would

like to emphasize that, you know, we — in working committees, I know how time pressures us in terms of we meet at lunchtime before and half an hour later, make the final draft. Because of time constraints, I do empathize with that, but when it comes to major decisions of tremendous impact, I really wish we had more raw data for us to examine for months ahead before we make a vote.

SNIDER: It brings up a broader issue related to what Dave and I were talking about yesterday. I mean, I think there are certain desirable behaviors we would like on the part of the various programs who come and present. Sometimes, we don't get the response that we would like, which is not peculiar to ACIP. There's other CDC business in which that also happens, but I think your point is well taken.

Perhaps one of the things we could do, John, is to be explicit when there is an action to be taken so that we get that included in the minutes, and that Gloria can compose a list — I certainly can make a notation — of actions that need to be taken after the Committee. Sometimes, it's not at all clear that a comment really implies an action; whether one is, you know, clearly requesting that a certain action be taken. So perhaps we collectively can do a better job of being sure that we don't drop the ball; that we clarify if there is a specific action that we're expecting from the program.

DEBUONO: I too am very grateful that we have a document that I think outlines the policies and procedures. I think that's terrific. I think we have needed this for some time and I commend the work of you all at CDC in putting this together. A couple of things — I think the procedural issue of resolutions, and votes and also the expectations that we all have relative to the process of resolution and voting should be in this document. I too would like to pick up on something that Chinh Le has said. I think when you have four out of nine in what should be twelve members on this Committee voting in favor of moving forward with the rotavirus document, I think that is not consensus. It may be a majority of those who voted because three of us abstained, but I think that's problematic. I don't think that that creates for the public, whether it's — again, practitioners or others — a feeling that this Committee embraced that issue. I think that's troubling.

I would prefer as someone who — I run a very large and a very complex agency. We have to go through a lot of procedures and processes involving a host of what are, in the New York State Health Department, 100 different committees and councils if you could believe that. We rarely have resolutions that come up ad hoc during a meeting. Our role as staff to those committees is often and almost always to have resolutions clearly identified, and written out scripted beforehand. We share that with committee members so that they know and expect that a resolution on

the following issues is going to be brought forth; here's what it is; and here's what you'll be voting on. So people come to the meeting knowing what they're going to be voting on.

There is always the opportunity for ad hoc, either a crisis or some urgent opportunity for a new resolution to be considered and brought up at the last moment, but we rarely allow that to be voted on at the committee meeting. That would come up at a subsequent meeting. I have concerns about hitting us with resolutions on an ad hoc basis during the meeting without the full opportunity to have a good vetting of material presented beforehand and the expectation that we're going to be voting on something. I think I would've benefitted from that.

MODLIN: It seems to me that I'm hearing from Chen and from Barbara that you feel like you were surprised that we were going to be voting on the rotavirus resolution even though a letter was sent to all of the members.

GRIFFIN: Well, the letter was sent three days before.

MODLIN: The letter that was sent to — I don't know how, I don't remember how long it took to get the letter out, but a letter was sent to members of the — the voting members of the Committee indicating that we would be considering the resolution, and that we would be making a decision at this meeting or would be likely making a decision at this meeting as to whether or not — to making a specific decision regarding the use of rotavirus vaccine.

HELMS: It was in a draft that came with the document.

MODLIN: There was a specific letter that went out over my signature as the Chair of the working group that we would be voting on this. Is that not the case? There should've been.

LE: It was dated January 28th.

MODLIN: Dated January 28th.

GRIFFIN: I think the other thing is it told us to pull out our old — and I thought that was rather insulting not to share the changes with us. I was in the midst of travel and could not get my old — so I think we all felt a little like we needed — I would've liked to have reread the statement and a little surprised.

MODLIN: You know, please accept my apologies if we haven't done this exactly as we should have. The intent, at least in the case of the rotavirus statement, was that there had been no changes since the prior meeting. Therefore, there was no new draft to share with you at that time.

Because of the need and the desirability of having the entire rotavirus working group in the same place at the same time, the only way which from an operational standpoint we could do that was to bring in the group the day prior to this meeting. It was the only way in which that was going to work. Unfortunately, because of that very, very short period of time, then the changes in the statement obviously occurred overnight and were presented yesterday, but I again, believe that the letter was sent to the effect that we would be making important decisions on this issue and to please refer to the prior document. Obviously, some of you feel that that was inadequate, and if it is, please accept my apology. We'll do better in the future.

DEBUONO: But my statements are more brought — I'm talking about the future, you know. My term ends in June of 1998. For the next group of people coming on, I think that it's very helpful in even the agenda to know, you know, that this is an — it says here "information, discussion, decision." I think it should be clear what the decision is going to be on. I think any resolution that's crafted should be shared with the Committee prior to coming to this meeting so that you're clear on what you're voting on before you come in.

SNIDER: Yeah. I think it is helpful. Certainly with VRBPAC, this is what's done. We get in advance, you know, what are the questions. I don't know if anybody has been around long enough that they remember, you know, how this agenda has changed over the past few years. What we have done is asked the programs, you know — I mean, it used to be just you had the agenda item and what time, and that was it. What we've asked the programs is — what is the purpose of the presentation? Is it to inform the Committee? Is it to discuss an issue? Is it to arrive at a decision? We've also asked them, although we haven't been tremendously successful in all cases, what are the questions they want the Committee to address? What are the key questions? I think, Gloria, we can probably modify the form one other way, and that is to say if there is — if there are resolutions to be voted upon that those be included. We can either include them on the agenda or as an attachment to the agenda. I agree with you. I think it would extremely helpful if we did that. I guess one thing I'd like to hear from the Committee is that if that information is not provided, shall we not include that on the agenda?

MODLIN: I think it might be helpful. We might practice a notice within the working groups. Obviously, once a meeting is over, you take your — all of your meeting material home, and you put it in one corner of your desk and don't think about it for a month or so. Then it comes to organizing the work groups and getting work done prior to the next meeting, and often that is put off until very late in the cycle prior to the next meeting, à la the rotavirus working group. I think it's happened with a number of the working groups so that the time available to be able to prepare meeting

materials and disseminate that information on a timely basis is obviously compared to sort of a — it's one of these human nature sorts of things. It may be worthwhile that we establish some sort of guide to the development of this — of the process whereby we may want to set a deadline for all work product.

SNIDER: Yeah. What we do — we have the deadlines for when these things are to be submitted, but again, they're not necessarily followed. I guess what I'm asking is, you know, I mean, I can make a decision as a CDC official that we won't bring something before you if it's not there by such-and-such a date. I have not been sure that that was, you know, the Committee's — the sense of the Committee, that that's what they would want me to do. So therefore, if the program has not done what we've already asked them to do to provide that information by such-and-such a date, we've tended to be somewhat lenient, you know, and not be — we have taken things off the agenda; don't get me wrong, but we've tended not to be too hard about it. If what the Committee is telling me is that they would really like me to be hard-nosed about this, if these resolutions aren't in, you know, such-and-such a time before the meeting that, you know, we won't include that on the agenda. Fine. Then, I mean, certainly it gives me more leverage with the programs to do it, but I — just like I have a sense of the Committee that that's what you'd like me to do.

MODLIN: Alright. Bob?

CHEN: Yeah. Let me just speak to that because I think part of the work that we do here, I think, will be amenable to that; part of it would not be. So for example, if some of the bird flu — avian flu investigations in Hong Kong had lasted a bit longer and Keiji kind of just got back more recently, I'm not sure he would've made that deadline; nor, for example, a few years ago in 1991 when we did the GBS study, the results were basically, you know, put together the night before the presentation. So I think we, you know, I think we want to give some rope or some flexibility not to be absolute about that.

MODLIN: I think there's no question whether the presentation, which will be informational only, where it's not necessary for members of this Committee to be prepared to make a decision, I don't see that there's any need to have any deadline, quite frankly. That serves the purpose of presenting late developing information, but I would agree that the Committee needs some time to study the materials that are available, perhaps do the necessary background reading and do some thinking, and perhaps even discussion with colleagues with respect to important decisions that need to be made and that shouldn't be made on the basis of last minute development of information. Fernando?

GUERRA: I think this is a tremendously important discussion and a couple of thoughts. One, it would be very helpful is, I think, we really develop these policy and guidelines for the working efforts of this Committee, and that there should be an opportunity to maybe have an orientation at the beginning of the term for some of the new members to introduce them to because otherwise, I think the learning curve is pretty steep and one has to really come up to speed very quickly. The other thing to do, and I think I've heard it several times around the table in this discussion, that there are so many things happening in public health and so many ongoing opportunities for making observations that are important for the work of this Committee. If there were an opportunity to bring things in at the last minute, maybe as add-ons, as long as one could have the supporting information that one needs and that one could provide copies to the members of the Committee for information, for discussion, for guidance to hopefully then get it on a more formal agenda in the future, or if there's need for taking some action at that time. I think that we need that capability built into this process.

SNIDER: Yeah. I don't think that would be a problem — sort of like an epi aid. I mean, you know, somebody — if there's an outbreak, they're going to deal with it. I mean, there does have to be some common sense. I was talking though more about the routine matters. I mean, often and even then though, we don't get the information that we'd like to have to provide to you — you know, to you in the time frames that we have already set. We've already set timelines for deliverables. The question comes up, "How are you going to, you know, actually make that happen," particularly when you have, as Bob was saying, you have people who are out of the country, you know. CDC staff, you know, if you find anybody sleeping or reading a novel or doing, you know, something, tell me about it because I've got some work for them. So I mean, it has to become a priority. I don't think, you know, there's any ill intent here, but you know, if we say that it is a real priority to get these issues, these materials out, and the questions posed and the resolutions written so much in advance of the meeting or it will not be handled at that meeting, then, you know, unless under, you know, it's under emergency circumstances, then I think it will happen.

MODLIN: Tom, you had a comment?

VERNON: May I speak to a — note a different issue?

MODLIN: Well, why don't — I mean, this is an awfully important discussion; others had comments about it. Stan, and we'll come back to Dr. Vernon.

PLOTKIN: I wanted to speak to a slightly different. . .

MODLIN: Well, why don't we finish up on this if that's okay. Chuck, and then we'll come back.

HELMS: Perhaps I'm the least able to comment on this being new to the Committee, but I'm impressed that — I'm pleased to be on it now that we have a set of procedures and deadlines, but that will be a step in the right direction, I guess. There were just a couple of observations — first timer — one would be clarity of outcome of discussion. I guess agreeing with Chinh here that it's not clear at the end of a discussion exactly what's been accomplished — to me. That might be helped by at the beginning having any resolutions that come before the Committee have to be in writing or something very close to that. At least on an overhead, it's quite clear.

The second is an enormous amount of time is spent word smithing. At a level of a committee like this, I think could be pushed a little bit into task force activity. Part of the issue of clarity too might be addressed by making it quite clear who's accountable for task force activity. I can understand from a staff perspective, having worked on staffs before, how difficult this can sometimes be, but it seems to me if there's a task force chair from the Committee, that that person should be the person in charge and responsible for anything that comes before this Committee from those task forces; that the process and so forth be improved that way rather than leaving it in the air and having staff unclear as to exactly what's supposed to be coming forward in what way or another.

MODLIN: We have in this Committee task forces; we call them working groups, of course, and they do a tremendous amount of work. There is a very close and constant interaction with the CDC staff, predominantly NIP, but certainly staff from other divisions within CDC. For the most part, this has worked out quite well, but you're right. The process can be — the focus on the process can be fine tuned. There's no question about that. John, do you have any further thoughts about this? Thanks. Dave?

FLEMING: Just looking from a sense of the Committee, I would also support more rigid deadlines that are in advance of the Committee. I think that we all look at what we perceive the deadline to be and do the work just before that deadline is. It seems that we sort of fall into a habit of people seeing the meeting date as being the deadline. So I think at this initial phase, we might have to be even more strict than we might be down the line about establishing the seriousness of the deadlines that would allow the Committee members to get this information before we come. It is frustrating and even a little insulting to come to a meeting and not know for sure what the issues are going to be until you're presented in a real-time fashion with this.

MODLIN: Let me ask you what a reasonable — you feel a reasonable deadline would be, ten days? Gloria, what do we do right now? Fourteen days is my recollection. You want to use the microphone, Gloria?

KOVACH: I have to mention to the Committee the staff is really improving. I mean, it was less than two years ago that I would be — well, maybe about two years ago — that I would be dropping material off at the hotel the night before for folks to read. So we are progressing.

MODLIN: Would it be reasonable just if they're out of disposal that the material be mailed no later than ten days prior to — be mailed no later than ten days prior to the meeting? Then you could set your own deadlines internally with respect to staff in terms of when you needed to prepare it, collate it and send it out. How do others feel about that?

KOVACH: Actually. . .

MODLIN: Fernando? I'm sorry.

KOVACH: I'm sorry. The request for agenda items goes out approximately twelve weeks before the Committee meeting. Items are due ten weeks before the Committee meeting. About seven weeks before the Committee meeting, we start to try to schedule where we go over it because this has to be published in the *Federal Register* fifteen days before the Committee meeting. It takes a week to get that published and a week for our committee management people to get that to the *Federal Register*. So the staff does know ahead of time. So I think we could work something out. We'd just have to be a little harder on it.

MODLIN: Barbara?

DEBUONO: I think it would also be very helpful and I'd like to suggest that at the end of each meeting, we have a sense of what is going to be coming up for the following meeting. I think that would help with continuity, both for the members as well as the staff to be able to say, "Okay. At our June meeting, we — at this point — it looks like we're going to need to be taking up the following issues for information, for discussion and for vote." I think that helps direct the staff as well to, over the next three months, focus in on the combination statement, the rotavirus statement, so on and so forth, again, understanding that there are going to be ad hoc issues that might come up in the interim. I think that would really be helpful for members and for staff to do that.

MODLIN: Tom, did you want to. . .

VERNON: Barbara noted earlier an issue that's long been of concern of the Committee and to others, and that is the number of people who must

recuse themselves from votes because of financial interests. This document can help a great deal in that respect because there is a great deal of confusion about what does constitute and what does not constitute a financial interest. One member of the Committee in noting a conflict of interest will note an unrestricted grant provided to his department in 1993 for a one-time project. Now there are other reasons why that member would declare a conflict of interest, but when this is quoted as a reason, it certainly suggests a breadth of complications from an educational grant which are not appropriately reflected in the documented.

Now I would point out that on page seven when the document does discuss "current financial interests and direct financial interests," there appears to be, to me at least, a need for clarity. I don't understand in reading it the different between "current" and "direct." Current has a timeline to it; direct does not mention a timeline. I bring this up simply to make the broader point that this is an area in which clarity is, I believe, especially important at a time when so many Committee members are not able to vote on critical issues.

SNIDER: Just a comment on that — we hope that at the next meeting, we will have the twelve members which are now approved. The procedures we've been instructed for selecting Committee members have broadened, I think, or likely to broaden the number of people who will be eligible to vote. For those of you who haven't been here for a while, we have — to be very frank — we have had some very difficult discussions with our legal staff here at CDC about how we should be interpreting conflicts of interest. We're not in full agreement here about how that should be done; nevertheless, we have to in the end follow what legal counsel — which is actually departmental legal counsel; CDC has none. We have lawyers here, but they actually work for the department and we have to follow what they recommend. So we will continue to have discussions with them about whose interpretations of these — actually, I wish we could use the approach that FDA does. I've certainly proposed that on occasion.

I think it's VFC that has particularly caused a great deal of problems because this Committee in essence, in contrast to any other advisory committee in government, in essence can make appropriations. There's a great deal of nervousness about the fact that we have an advisory committee that can, has been told by Congress it can make appropriations. Therefore, I think the "strong conservatism" — if you will — of the legal counsel is somewhat understandable. Yet, I think it does get us into — has gotten us into some difficulty. I think we are trying to make some changes with regard to the constitution of the Committee to make changes there. In addition, we also found that we can — it's our option of whether ex officio members can or cannot vote. One option we have is, in difficult situations, if there were to be — again, I hope there

never will be — but if there were to be another one of those situations we ran into where, you know, we had three to one votes or something like that, we will be able to have other people here; mainly ex officio members, if they choose, can become voting members if a quorum is not voting — eligible to vote.

MODLIN: Who sets decisions, Dixie, at that point in time? Who decides whether three members, or five members or seven members are a quorum for the purposes of voting, particularly for VFC issues?

SNIDER: Well, I guess I would have to make it in the end, but I would have to consult legal counsel here — Kevin Malone.

MODLIN: Okay. Mimi.

GLODE: I've been concerned about the small number of people sometimes eligible to vote. I've been concerned also about despite these instructions concerning conflict of interest, they really don't cover the multitude of various issues that arise. I would personally feel a lot better not trying to make a personal decision about whether I have a conflict of interest or not, but rather disclosing everything that falls under any category and having an independent legal authority, you know, determine that so that we're all comfortable that we're all being consistent with regard to that. I sort of go back to the FDA policy of I'd like to be faxed — two months before we're meeting — my last financial disclosure statement and say, "Is this still accurate," or "Please update if it's not." Then a decision can be made about granting waivers, not granting waivers. I mean, we put on a course and we get educational grants for that course. I've never thought that was a conflict of interest, but someone else might think it was, should be for me or is for them, and therefore doesn't vote. So I think that process still needs to be further improved, clarified, made consistent. At the time of a vote — and I strongly support a one-month or something deadline because I agree that if you tell people the deadline, they will get close to it — for any resolutions that are going to be voted on and everybody assess those resolutions so they know, and at the time of that formal vote, then I would also recommend that we clarify who is eligible to vote on this issue, "Fine, that's X number of people. Now let's take the vote."

MODLIN: Jane.

SIEGEL: In terms of the number of people voting, I think it would be important to spell out what the needed number of voting people available to carry out a vote is after disclosures, after absences so that everyone knows that if we don't have X number of people, we can't carry out a vote.

SNIDER: It should be written down.

MODLIN: Other comments?

SNIDER: And the other thing I should point out that we have made a change as you will note. In the past, we have had some people who accepted membership on the Committee, but haven't attended even half the meetings. We have now set down in here a rule if an individual misses a certain number of meetings, then they will be asked to resign from the Committee.

MODLIN: Other comments?

DEBUONO: I think Dixie raised an interesting issue that I think does beg the question and requires clarification, and that is the status of the ex officio members. Sometimes, they're ex officio members without votes; sometimes with votes. I think that should be absolutely clarified and, you know, you've got seven listed here. That adds to twelve, you know. If all those seven can vote, that's nineteen. That changes the dynamics of everything. I think it should be absolutely clear if those people — this should be in the statute, frankly, whether they have a vote or not. If it's not in the statute, it absolutely should be in policy. It should be made very clear whether they have voting rights or not, and what they can and can't vote on: VFC issues or merely ACIP statement issues. That's a procedural question that is critical to this Committee. I never believed or thought they had voting rights. If they do, fine. I just think we ought to know exactly what the story is.

SNIDER: I think Kevin's intent was that they would only vote if we did not have a quorum voting. That would be. . .

DEBUONO: I think, and that also speaks to what is a quorum, you know? With VFC, we've had two to one votes on things. The next thing you know, a vaccine is now put in the VFC program. Is that adequate?

SNIDER: My understanding is that a quorum voting would be six or twelve members, five.

DEBUONO: I think all of that is going to need to get spelled out. I think the Committee members ought to have that.

SNIDER: We could ask Kevin.

DEBUONO: We've got to get oriented to that. Perhaps in June we could have. . .

SNIDER: Otherwise — just to fully clarify on the ex officios — otherwise, we do not anticipate ex officio members voting. It's only in the circumstance in which there is not a quorum.

MODLIN: Barbara, please send all your suggestions to Dixie; same thing with you, Mimi. If you would do so, they obviously will find their way to the right person as to the best way to deal with this. Then in this way. . .

SNIDER: Or write suggestions on the document.

HALSEY: One area that was a source of confusion for me when I was a regular member of the Committee — and I think it's still a source of confusion for FDA in some settings having just participated in one of the advisory committee meetings — for those of us who are in supervisory positions over other faculty at universities or health departments who are supervising other people within the department, there are sometimes grants that come to those people who are below you in the hierarchy of your institution. Does that constitute a conflict of interest for you or not? It's spelled out that another grant to the institution, you know, some of that is here, but it is unclear if people who, you know, are directly under you have a conflict, does that mean you have a conflict and under what circumstances can you vote and can you not vote? Maybe you know the answer already, Dixie.

SNIDER: I mean, I don't want to give an answer without consulting counsel.

MODLIN: It might be worthwhile to actually pose a few situations such as that and actually have them explicitly spelled out, say, with examples which I think would help to clarify this if when we get around to expanding this section.

SNIDER: Send me a list, and we'll send the list over to Kevin and see if we can get some written responses.

MODLIN: Florian.

SCHÒDEL: Florian Schòdel, Merck. I just wanted to comment on page eight, number eight, which I think exemplifies that examples aren't necessarily so good either because here you have "a restriction to vote on additional doses," but you have no restriction to vote on less doses and the contraindication. That doesn't seem to make a lot of sense to me. On page five, number two, I think the first paragraph. . .

SNIDER: The first was on page eight?

SCHÒDEL: On page eight, under eight you say — you have two examples here. You say, "for example, votes to recommend additional doses would be subject to the recusal restriction. On the other hand, no restriction will exist on votes pertaining to the list of contraindications." So you can vote on giving more doses, but you cannot vote on giving less doses because something is contraindicated.

MODLIN: Why don't you point those out to Dixie during your break or afterwards? We'll just make sure this is a little bit of word smithing, but thank you. Fernando, did you have a comment?

GUERRA: Yeah. This is so important. I wonder if we couldn't set some time on the agenda in June to maybe sit down with legal counsel to specifically go over some of these questions in some areas that I think will be evolving as we give it some thought, but I think that having the opportunity for some interaction could be very helpful. I guess it could be done as a totally separate work session or it could be done during an open meeting.

MODLIN: I think probably it would be appropriate to do during an open meeting. Maybe we could set aside 30 or 45 minutes on the agenda for next June to do so. That's a good point.

GUERRA: It might need an hour and a half.

SNIDER: Well, like I said, I think that's a good idea. I still think it would be very helpful to me if you could give me your questions, just all of you — anybody in the audience — pose those questions and give them to Kevin, and have him come up with some written responses to those questions, but then we could have a discussion of it because I think I can't give the rationale for some of the things that, you know, have come up. I know what I've been told; that this is the way, you know, it should be, but I don't always know the rationale for why they came up with that particular interpretation.

MODLIN: If you have specific suggestions or situations as Neal had suggested, but again, ask people to submit those for — that will be points for discussion. Stan, you've been very patient up there.

PLOTKIN: I have two quick suggestions as an observer: one is that at committee meetings that I've participated in, I've found it very helpful at the end of the meeting to have somebody with a transparency, an overhead and a crayon simply write down — after, of course, having gone through what was done — write down the conclusions of the meeting and show that to the Committee so that everybody agrees on what was actually done. The second point is that there is a lack of uniformity as far as presentation being available to people who are not on the Committee — now that is to say slide presentations, transparencies. I can understand why working documents might be confidential to the Committee, but public presentations of data in a public committee are perforce not private, and therefore, they should be available to people if. It's considered too onerous to have them at the time of the meeting because do it at the last moment, there could at least be a sign-up list for people to request copies of the slides.

GRIFFIN: I think one of the things we were faltered on with the polio was the policy analysis as Dixie mentioned. I like having that in here, but I think we're really not used to going through that process. I think one of the things that bothered me about the rotavirus was I don't think the alternatives were — like what are the alternatives to universal recommending routine vaccination? Are there any alternatives? It seemed like the alternatives we came up with were objectionable because that would mean that kids who couldn't afford it couldn't get this vaccine, but there may be other options. I just was concerned that all the options weren't laid out. The other was that it mentions in the policy analysis to make sure you have identified the stakeholders and know what they want. I think that we haven't really used this step-wise approach.

ZIMMERMAN: The program people don't have this approach.

GRIFFIN: Right.

SNIDER: That's what I meant when I said we don't have any policies and procedures.

GRIFFIN: Right. So I mean, I think it might be just useful to go through the rotavirus with this sort of framework of policy analysis.

SNIDER: The reason I was wanting just clarification — get some endorsement even of a document we know is going to change from the Committee to go ahead and begin to use what we have just because there is a lot of good stuff in here. I'd like to be able to go ahead and tell the people on our staff, the people who are with the working groups that this is the way we're going to do business because up until this point in time, it's just been, you know, an exercise of a work group; never gotten any okay from the group. By the way, Stan, Gloria says we do have a sign-up list for the materials ready. They are mailed out for those who sign up.

HARDEGREE: As someone who frequently sits at this table and asks about what data is available, I'm delighted to see page ten and the information on pages nine, ten that relate to this. In view of the comments that have been made about whether or not you could go ahead and get started on this, I think having such a strength of the data spelled out would be important as we move forward in developing new statements. I'm wondering if the rotavirus statement will be developed using this kind of information. We went back and forth yesterday about something about expert opinion.

SNIDER: Tell the BMT people. I was very impressed to see their's. It was nice.

MODLIN: It is a narrative on the statement as well or it is being incorporated into that. It certainly was there at the last iteration. John, last word.

LIVENGOOD: Yeah. I want to come back to conflict of interest a little bit. I think I heard some from Tom and a little bit from Mimi is that while I certainly don't want people with conflicts of interest, we have evolved into a position where people disclose things that I don't think probably are conflicts of interest. Certainly when I go out, I hear a lot from anti-vaccine forces. They all have conflicts of interest; they're all in bed with the manufacturers, you know. It's not a good process. So I mean, if some balance could be made to the process by which people reveal conflicts of interest, I mean, non-restricted educational grants. I know we at CDC sometimes say, "Well, let's travel our own people to participate in that to avoid a conflict of interest because we purchase so much," but I don't think we need to get so carried away that eventually nobody can not have a conflict of interest through something that clearly is not directly related. I know Kevin and I sort of disagree on this, so I won't say more with him not here to defend his own point of view.

SNIDER: As you know, I do too.

MODLIN: Yeah. Dixie, you certainly have a consensus support for this statement.

SNIDER: Yeah. I think so and I think that it makes it — as Fernando had said — I think it makes it even more important to engage Kevin. I think it's important for the Committee to engage Kevin on these issues, both for educational purposes as well as for hopefully the possibility to have some kind of, what I would view as a little bit more rational articulation of what this is.

MODLIN: Fine. We will try to put that on the agenda for June. In addition, in terms of the interest of anticipating what else may be on the agenda, we certainly will try to have a final rotavirus statement to vote on for the Committee. There will be a final statement on the combined vaccine group — or combination vaccines. I anticipate probably an initial report on Lyme vaccine from the working group that Dave Fleming is chairing. I'm sure there are others, but those are what come to mind right at the moment. Fernando?

GUERRA: We have to be sure about the time that is allocated for the discussion of legal counsel will be enough and ensure that, you know, 45 minutes or an hour may be enough. It may be a little longer.

MODLIN: With everything though, I think that we'd ultimately wind up having to jockey for space.

GUERRA: Sure.

MODLIN: We never or you rarely have time to discuss everything. We'd have to make some decisions regarding priorities amongst items that are

submitted for the June meeting. Of course, we'll have to do the same, but I agree. This is an important part.

SNIDER: We may be able, and I think we ought to shoot for it, is to get some written responses to the questions you submit, and then get that out to you in advance of the meeting which may cut down. . .

GUERRA: Cut down on the time.

SNIDER: . . .on the time we need for discussion.

HELMS: John?

MODLIN: Yes, Chuck Helms.

HELMS: I think Barbara's comments are important, particularly about defining what a quorum is and so forth. I think that's something we could almost get some options for next time. Rather than discuss things in vagueness, maybe discuss things in terms of what defines a quorum for this Committee; what is this and what is that; who votes, who doesn't vote.

MODLIN: I think Dixie heard you and I think this is to be discussed with Kevin, with counsel. That may be one other agenda item that we can bring up during that discussion; I agree. Let's take our break. Let's try to be back at 11:30, please.

We can't get started until we have at least one more member. There's Chinh Le I can see in the lobby if somebody would yank him by the tie. There we go. The next presentation will be on the Vaccine Identification Standards Initiative. Dr. Bruce Weniger will make — will introduce the topic.

WENIGER: Thank you. One of those problems that we're going to be addressing briefly and that's for your feedback is about one that cuts across and affects many constituencies and components in our immunization system in a very broad sense; that is the transfer of data from the vaccine vial into the medical records, into the immunization registry. From the point of view of many different stakeholders in our system, this is an important topic. From the registries' point of view, they only can function as well as the data that goes into them. This includes the types of computer programs you heard this morning about that determine whether a child is immunized and what shots they need. That only works if the data that's plugged into them is accurate.

The practitioners — from the practitioners' perspective, they are terribly overburdened with the recordkeeping responsibilities related to vaccination and are looking for solutions to improve that. The FDA is

thinking about ways to improve the labeling and packaging of pharmaceutical products to minimize errors that occur in their administration. They just had a meeting last month in Washington about this. From our own self-interest in the Vaccine Safety and Development Activity, since we are responsible for national surveillance of the adverse effects of vaccines and side effects, we're affected by the increasing omissions and inaccuracies in the systems that we need to do that job and maintain public confidence in vaccines.

To serve as a catalyst for a number of potential solutions to these cross-cutting problems, we have volunteered to try to organize an initiative and we've brought on board Joshua Schwartz, who is a Vaccine and Development Fellow with us for one year in the Vaccine Safety and Development Activity. He will more formally describe what we've been doing and some of the ideas that are proposed, and then open it up for feedback from the ACIP. Joshua, please.

SCHWARTZ: If I could have the lights, please. Good morning. As you all know, the National Childhood Vaccine Injury Act of 1986 requires the immunization provider to record in the patient's medical record the date of vaccination, the manufacturer and identity of the vaccine, the lot number and the name, address and title of the person administering vaccine. Such records provide the essential information needed to identify the exposures to specific vaccines to allow high quality surveillance of vaccine, safety, efficacy and coverage which are essential to maintain public confidence in our immunization programs. The accurate transfer of vaccine identifying information from vial to medical record and into immunization registries is becoming increasingly problematic. New vaccine products are entering the market with longer names and increasing number of antigens in combination vaccines, and the task of describing such information is becoming increasingly burdensome on health care providers.

One study evaluated the accuracy of computerized immunization records transcribed from handwritten records of 2,098 children vaccinated at UCLA Children's Health Center over a twelve-month study period. The overall transcription error rate was found to be at least 10.2 percent. Moreover, it was found that 38.4 percent of the children who were determined to be under-immunized from the records had previously received undocumented immunizations from other providers outside of the UCLA system. Here at CDC, the Vaccine Safety and Development Activity of the National Immunization Program is responsible for two major national vaccine safety surveillance systems. In the Vaccine Adverse Event Reporting System or VAERS — a passive surveillance system we run jointly with the FDA — preliminary analyses have found substantial rates of missing or erroneous data in the provision of lot numbers and other identifying information on adverse event report forms. You can see

in this slide here that the proportion of VAERS database records with missing lot numbers has increased steadily from about 12 percent in 1993 to about 20 percent in 1997.

When the lot number is present, its inaccuracy is also increasing. Here you can see that the proportion of VAERS database records with suspect lot numbers increased steadily from a low of about 9 percent in 1992 to about 14 percent in 1997. Since the actual vaccine lot numbers in circulation are proprietary information not available to CDC, inaccurate lot numbers are defined as those received on fewer than five VAERS reports from among the approximately 10,000 received each year. Obviously, this may artificially inflate the number of reports defined as inaccurate for new lots that have just entered the market before the cut-off of the analysis.

The active surveillance Vaccine Safety Data Link Project, known as VSD, is a perspective cohort study in which collaborating HMOs provide computerized records of all immunizations and all medical events on a population of children representing 2 percent of the U.S. national birth cohort. This line listing here contains the first thirteen lot numbers output numerically from the database for a single vaccine. These are the lot numbers and in this case, it's a Connaught DT vaccine — the most frequently lot numbers accompanied by various similar ones. You can see this lot number here, OJ21027 used for 95 shots; then OJ2102 differing only in that it leaves off this 7 here was used in only one shot, and OJ21017, again using only shot differs in that this 2 is a 1 in this case. Now these numbers used only once probably represent reading or transcription errors from a total of 1,585 immunizations with this vaccine; 13 of the 104 lot numbers were reported to have been used for more than 10 vaccinations each. Alternatively, 91 of the 104 have been used with 10 or fewer vaccines each.

In other analysis not shown in this slide, Wyeth-Lederle was kind enough to provide their lot numbers for DTP vaccine in circulation. It was found that 19 percent of the lots recorded in the VFC medical records did not exist. It's easy to see how transcription errors can occur. Sometimes the lot numbers are embossed are plastic without any ink in tiny letters that are hard to read as on this individual dispet of oral polio vaccine you can see somewhat the lot number here. The multi-dose package sometimes does not offer much help to the harried nurse rushing to complete the paperwork. In this case, both the lot number, slightly different now from the one on the dispet located here and an extraneous control number — this number 12 — are embossed on the packaging. If the nurse can make out a number here, it's quite possible it will be the wrong one.

Even on cardboard packaging sometimes, lot numbers are embossed without ink as shown here, which may be difficult to read correctly under

certain lighting conditions such as these. Confusion can also arise for vaccines like this DTP-Hib for which two separate vaccine boxes are contained in this larger box shown above. The nurse mixes a DTP vaccine in the box on the left with the Hib on the right. Notice that there are three different lot numbers provided for what would be a single vaccination. If either are the bottom two are the one that's recorded, can we ever be sure exactly what the child received? To try to address these problems, we are coordinating the Vaccine Identification Standards Initiative, or VISI for short, to develop systems and standards to improve the accuracy, efficiency and user friendliness in transferring essential vaccine identifying from the vaccine vial into the medical record. These improvements could streamline the recordkeeping process and thus encourage providers to voluntarily participate in providing data to immunization registries. This is a voluntary cooperative effort among relevant parties in the immunization community, including FDA, vaccine manufacturers, professional medical organizations, state health immunization programs, the immunization registries, medical records software providers and others.

In an initial telephone conference call and a face-to-face were held here in Atlanta last October. The next call is scheduled this month on the 20th. At the first VISI meeting, an AAP pediatrician described immunizations as typically occurring in an atmosphere of "controlled chaos." This sentiment was echoed by other providers at that meeting. Another challenge would be to work with existing and evolving standards for health care product packages, immunization registry communications and others. Reducing the burden of recordkeeping is clearly a principle goal of this initiative. Indeed, the American Academy of Pediatrics passed a resolution in 1997 proposing peel-off stickers on vaccine vials, which is one of the strategies we're pursuing here. Another area is to develop standards for bar coding the information on such sticker, as well as on vaccine packaging. For those providers who have computers in their offices, scanning bar codes is now quite inexpensive and virtually eliminates the commission of transcription errors.

To improve the transfer of information contained on stickers, it would be helpful if stickers were of a standard size that could fit onto a uniform immunization medical record form — a copy of which could be faxed, mailed or scanned, sent electronically to an immunization registry. Finally, for providers who lack computers and fancy equipment and must rely on reading and manual recording of information, the required vaccine information can be provided on the package in a standard format. We've all become accustomed to the nutrition facts panel on food packaging. Can a similar panel be designed for vaccines? Also, can the format of lot numbers be standardized across manufacturers embedding letters that intuitively identify the manufacturer and the type of vaccine without resorting to an arcane code sheet.

To illustrate a few of these strategies, here's a U.S. vaccine with a peel-off label, which can quickly be peeled off the vial and placed into the patient's chart. This convenience can be provided for cat vaccines as seen here. This is feline leukemia. Why not for vaccines for children? So we developed a prototype sticker for a vaccine with the most complicated and challenging nomenclature now used for children. The full generic name for TriHIBit vaccine is twenty words long. So this peel-off sticker leaves it off, but it does provide the manufacturer's identity and a proposed standard abbreviation for the manufacturer in this case, PMC, also, an abbreviation for the vaccine type, DTaP-Hib. Standardized abbreviations for vaccine manufacturers and vaccine types are being considered as useful components of this initiative. The prototype label also provides the national drug code which uniquely identifies the manufacturer and vaccine type. It also includes a bar code for the lot number and for the expiration date.

Many ideas have come from samples of vaccine vial peel-off stickers from European countries requiring them. This is an example that I got from Sweden recently. Those are two peel-off stickers here that actually have multiple layers so that the information can be placed in different records. Another idea is a vaccine information panel as I mentioned before for the vaccine package in which all the key information that a nurse or doctor might ever want or need can be provided in a standard size font and location on the package. This idea, again, is based on the success of the nutrition facts label which we read in the supermarket aisle and on which we can quickly identify the calories, the fat, sodium and other information that we're interested in. A prototype just developed for discussion at the next VISI conference call is this draft uniform vaccine administration record, which includes most of the data already collected on the existing American Academy of Pediatrics form, but rearranges it. Copies of this form were distributed and should be available on that table in the back if you'd like to see one.

This form permits either writing the vaccine identifying information by hand in these fields here surrounded by the thick gray boxes, the manufacturer with a code, the type, and the lot and the expiration date or by using a peel-off sticker, as you saw before, once the manufacturers begin providing them. This sticker concatenates all the needed information — identifying information rather — into a single string for scanning. As this initiative proceeds, we would welcome participation and feedback from ACIP members, and the organizations and institutions they represent. Thanks very much. Bruce?

WENIGER: Thank you, Josh. We would most welcome maybe turning up the lights and getting some feedback from the ACIP members, and perhaps even consider the possibility that the ACIP could designate to relate with this

initiative, participate in future conference calls and face-to-face meetings, and get the guidance from the broad constituencies represented on the ACIP. Thank you.

MODLIN: Thanks also for a nice and concise presentation. Comments? Did you have a comment, Rich?

CLOVER: This parallels with the algorithms initiative because one of the hardest parts of that initiative is recording in this information that is easiest to duplicate. So to have standards and have a mechanism where you can bar code it in would simplify that. One of the issues with bar coding though is someone does have to enter the data. How would you suggest that the data be entered? Would that be left to the individual registries or would you do it centrally and download it to the various registries?

WENIGER: Well, at our first meeting in October in Atlanta, we heard two possibilities: one is that in those practices that are already somewhat computerized where the patient's record is already on the computer screen, when vaccines arrive in the practice, the available lot numbers that are in the system are entered in. So a nurse could just simply up-scroll or down-scroll on the screen and click on the proper lot number that she reads off the vial, or if they have the scan wand, he or she just reads it across the actual vaccine the child gets and it's automatically input into the electronic system. Then the peel-off stickers are unnecessary and so everything is electronically captured. If you have a practice that doesn't have that kind of equipment, the concept would be you'd peel off this thing and stick it on the — one copy on the medical chart, another copy on a standard — well, this could be the chart form as well as the immunization record form. Did that answer your question?

CLOVER: Well, I guess I need education. I think the bar codes — you have to make the bar codes to a data set and that data set has to be written and established.

WENIGER: Well, you have to link a child, who may have his own code or bar code, with the vaccine. So at some point, either manually or by peeling off the sticker, that information of what vaccine you're giving has to be linked to the proper child. So that could be by placing it in a form with that child's name on it or when that child's record is on the screen, choosing the appropriate one or a combination of those.

LIVENGOOD: The bar codes themselves are essentially assigned.

WENIGER: Yes. The national drug code is assigned by the FDA when a vaccine is licensed — when all pharmaceutical products are licensed. With that you get unique information about the manufacturer, the vaccine type and in addition, the last two digits tell you the packaging formulation, whether a

unit dose vial, or ten-dose vial or whatever. So there are multiple NDC numbers for the same vaccine from our perspective. So software providers would likely have to have a little look-up table among the maybe forty or fifty different products. The NDC numbers might have to convert to a different number that's transmitted electronically, but that's a fairly simple thing to do within the software.

LE: I don't know how much feedback you want on this form right now, but just a couple ones if you want, you know. In the right upper corner box which says "parent/guardian initials," it would be nice to perhaps say something like "VIS given" and then the parent or guardian signs right there because that's also a regulation, a dilemna of how much to clutter the medical chart with signatures and so on. If we just — and because by law, we have to provide the VIS. It would be nice with the initials to say that the VIS is given there. Another thing too, the less the nurse has to provide things, then the better it is. In terms of the site, which is the column where you have "LTM" as an example, perhaps a check box or something would be great. Then down at the bottom, way down at the bottom right corner, I'm not sure why you didn't need that box. I don't know whether you have it.

WENIGER: Well, many of these boxes were simply borrowed. I hope there's no copyright problem from the AAP form. I suspect that these issues were discussed carefully there, but these are very good suggestions and we do welcome and solicit feedback now or in the future on ways to improve. This is basically version number one of what will likely be many, many drafts before we achieve harmony. I guess to make a comment, I think there are already vaccine manufacturers such as Merck that are putting peel-off stickers on some of their product formulations like the pre-filled syringes with hepatitis A vaccine, I believe, in this country. What would most energize this whole solution it appears is to have a common standard because it wouldn't make sense for Merck to have a sticker that's of one size and shape with the location of certain pieces of information, and another manufacturer to come up with their own version that we're not compatible. What we see as a role of this initiative is to try to achieve a common standard because once that happens, whether it's with computer modems, or with software or whatever, then things can really move more quickly in terms of getting improvements in the system. We certainly welcome these ideas and Josh, as I can see, has been writing them down, and so a lot of further discussion obviously on all of these that will take place over the next months and years probably.

MODLIN: Dr. Gilmet.

GILMET: One other thing to think about if you haven't already would be putting ICB-9 codes on this as well for payment purposes. So it could also be used in that context.

WENIGER: Do you mean ICB or CPT?

GILMET: For CPT, I'm sorry.

WENIGER: Well, we've — that idea has been broached. One obstacle which may be can be overcome and we can — and AMA did send people to our meeting in October — is that CPT codes are copyright and protected. One cannot simply use them without the permission of that — of the AMA. So that would certainly be something to add to that vaccine information box.

LIVENGOOD: Well, you could develop something that would link the vaccine that you scanned in to a CPT code; I mean, a little module.

WENIGER: Well, in the software, the software people would say it'd be very simple if you only have thirty or forty possible NDC numbers in the software of the provider's office or at the immunization registry. It can automatically convert this number to whatever CPT code is necessary. So those things are relatively easily handled in the software, but it certainly seems to me a useful thing to put in that vaccine information box if the AMA would permit it without charge.

MODLIN: Thanks very much for a very nice presentation. You'd ask to have a representative from the ACIP participate in the process. I believe I saw Rich Clover raise his hand.

CLOVER: It's kind of like an auction.

MODLIN: He was the only one who moved. I think we'll designate Rich as a very able individual to help you out. Let's go on to the next item on the agenda, please, which will be a topic that was introduced at the last meeting. Bob Chen is back with some more information alopecia associated with hepatitis B and other immunizations. I would point out that this is an item that does require a decision by the Committee.

CHEN: Okay. Some of you may think this is actually just a jacket. It's the latest in fashion body armor. After yesterday, I realized I'd need a little more protection. I think the last few meetings we've been talking more and more about vaccine safety issues. I think in part that really reflects the surveillance system that as we successfully reduce our cases of vaccine preventable diseases down to fairly low levels, the vaccine adverse event reports to the VAERS basically at this point kind of outnumber our total of our traditional diseases. Clearly, the way forward is to try to figure out which of these reports are actually coincidental events and which ones are really new to vaccines. Then yet if they're really new to vaccines, what is the actual attributable risk? Then if they are actual risk factors in pathophysiology that we can understand if the disease is not eradicable,

then perhaps we can go back to the basic science and make a safer vaccine.

Along those lines, I think many of you know that over several years, we've been working with our FDA colleagues to develop the VAERS system and then the Vaccine Safety Data Link as a kind of a complimentary system. Over the last year and a half or so, Bob Wise at FDA has been working on the signal of hair loss after immunization, which he summarized in a nice *JAMA* article recently. We were going to try to link Bob up in Invision so that he could make the next introduction. Bob, are you on the line?

UNIDENTIFIED SPEAKER: Bob's not here right now. We expect him in about five minutes, but go ahead, proceed.

CHEN: Okay. Well, he — I guess we must be ahead of schedule, in which case then what I'll do is I'll — since you have the article in your hands and if there are any further questions in the Q&A, Bob will be here. So when this signal, if you will, came up from VAERS, we said, "Well, let's put it to the test. Let's bring it up in the Vaccine Safety Data Link Project and see how quickly can we get an answer in terms of either confirming it or denying it, putting an attributable risk figure on it." Steve Black from Northern California Kaiser has been kind to join us this morning to show the program preliminary results from that analysis.

BLACK: Thank you, Bob. Good morning. As Bob stated, when these results were published this fall, we decided to take a look at the data from the Vaccine Safety Data Link at two sites which had outpatient data: Seattle and also the northern California center. This work involved a large group of people over about three months to try and take a preliminary look at this. I wanted to say that this is a work in progress thus far. First of all as you can see here, the initial signal came from VAERS. What we did initially was to take a look at automated data only using automated exposure information for vaccines and then linking that with outpatient diagnostic codes from the two centers. As you can see here on this overhead, the initial result identified several hundred cases of alopecia from automated data and did not show a significant association with receipt of hepatitis B vaccine. These results are, I should say, are in children eighteen years of age and under were not looked at at all.

So what we then did at that point is we did a retrospect of matched case control study at the two sites with outpatient information. In northern California, this used data from 1995 only, like I said, with the data set that was not readily available, and in Seattle, used data over several years. Patients with visits for hair loss — all cases from the automated data — were identified. Five controls were assigned for each case. A detailed chart review was undertaken to confirm and further classified alopecia

diagnosis. The vaccine data from the HMO immunization databases were used for exposure information. So this is an initial overview here. You can see a couple of things. Thank you. As you can see here, these are from the two sites in Group Health in Seattle and from Northern California Kaiser. There were a total of 392 cases in northern California and 130 from Group Health. Their analysis only went to age seven, whereas the analysis in northern California went through age seventeen. It's interesting that a majority of the cases tended to be identified in females. Next overhead, please.

Some of these cases were excluded from our primary analysis that I'm going to show you although we've since done, and I will show you, as well as supplementing all control cases. The initial analysis we did excluded cases which had an underlying cause of disease which is shown here to just bungle infection, traction, pressure, chemical, et cetera. This is an initial overview here and let me explain the format of this slide because we'll see it in several of the others that follow. This is just an unmatched summary here. What this explains is for an exposure window of fourteen days or sixty days in the two sites — what percentage of cases was vaccinated within different age groups, and what percentage of controls was vaccinated. You begin to see some suggestion of a signal here although none of the signals in the data that I'm going to be presenting to you was significant. You can see that in the ten to seventeen year old age group in the fourteen-day window in this analysis that there's suggestion of a three-fold increased risk, but that is not significant. Next slide, please.

This is an analysis employing the matching. You have more — there's more paper in your hand-out than there is that I'm going to have time to show. This analysis here employs the matching and looks within seven, fourteen, thirty and sixty days following receipt of vaccine has exposure window and then identifies a risk ratio, a 95 percent confidence interval and a p value. You can see that none of the ages on this analysis is significant and that there is, in fact, the risk ratios are less than one in the thirty- and sixty-day window. Next. We then undertook within a fourteen-day window since this seemed to be most suggestive in the prior table to then break this down by age. That was done to the sixty-day window as well. As you can see, again as we saw on the unmatched analysis in the fourteen-day window in the older children — the ten to seventeen year olds — there is an elevated risk ratio, but that again is not significant with a p value of .13. When we looked in the larger time window, there is really not — the p values are quite unsuggestive of any association.

Now one of the things that was suggested when we shared this data with Bob Wise amongst others was that perhaps, although the physicians were identifying a cause of alopecia such as traction or whatever, that maybe they were just doing this because they were not thinking of a

possible other ideology which could be vaccine or something else. It was suggested that we might look at all, sort of all cause alopecia in this type of analysis. This is presented here in this overhead. You can see that within seven, fourteen, thirty and sixty days, again the highest odds ratio is within fourteen days although that's no way near significant. Next slide. If we focus down on the fourteen-day interval and break this down into different age groups, again in the ten to seventeen year old age group within a fourteen-day window, the odds ratio — I don't know if you'll remember — but from before, was 3 the estimate and that comes down to 2½, but because of the larger number of cases involved here, the p value actually is a little bit lower, .09. It's still not significant.

So that's pretty much the data we have to date. I want to say that this is preliminary. We wanted to try and calculate an excess risk or a risk that might occur in this group at the 95 percent bound in association with the vaccine. This number is 8.2 cases per 100,000 doses of hepatitis in this age group. So another way of putting this is we're 95 percent sure that if there is an excess risk associated with hepatitis B vaccine, that it's 8.2 per 100,000 or less. I want to emphasize it could be a lot less; it could be zero, but this is the best that we can do with the data that we have thus far. So in conclusion, we conclude at this point that this study did not demonstrate a statistically significant elevated risk of alopecia following hepatitis B vaccination in children, which this study was limited to. Further studies will be undertaken to both expand the cohort and to look at older individuals. Thank you.

UNIDENTIFIED SPEAKER: Bob Wise is here at Parklawn. Bob Chen?

CHEN: Yeah.

UNIDENTIFIED SPEAKER: Bob Wise is here available for comment.

CHEN: Okay. Bob, did you want to highlight certain features of the initial signal that it, you know, they looked at in the six to ten year old? Can you hear us, Bob Wise? We may or may not be having technical difficulties. Rarely do we have actually have kind of a unique clinical syndrome or unique laboratory findings associated with the damage. It appears in several of the cases, we have a situation where the patient lost his hair after vaccination. The hair grew back and then ultimately though, the hair fell out again.

MODLIN: Let's try again and see if you can't. . .

CHEN: Bob Wise, can you hear us now? Bob Wise?

UNIDENTIFIED

SPEAKER: We can't hear you.

WISE: We can't hear you, Bob.

MODLIN: Chinh?

LE: Steve, since the study was looking mainly at pediatric age groups, were you able to look at whether those children received all the vaccine around the same time or whether the copesynergistic effect of two different vaccines may change the data or observations in any way?

BLACK: We had a chance yesterday to review the charts of the adolescents. Almost all of them had repeat hepatitis B as an isolated injection in most of their exposure. About two-thirds have received TB in one of them, but not necessarily in others. The other thing I neglected to mention is that the alopecia in all of these children resolved or there were not any of them left with residual problems.

MODLIN: Why don't we wait until we get the audio problems sorted out. Are we okay now? We're obviously getting some feedback. Do you want to try again to see if they can hear us at Parklawn?

WISE: Yeah, we can hear. We can hear you now.

MODLIN: Terrific.

CHEN: Okay. Just to summarize what we've done. . .

WISE: That microphone's not working. Bob Chen, that microphone is not working.

MODLIN: Maybe that you actually need to use this mike, yeah.

CHEN: Okay. Can you hear me now? Okay.

WISE: Yeah, that's better.

CHEN: Bob, and then I highlighted from your paper the positive rechallenge phenomena which basically suggested to us that a causal situation is going on. Is there any other major points that you wanted to highlight for the Committee?

WISE: Well, okay. Yeah. Basically, I think you all — can you hear me okay?

CHEN: Yes.

WISE: Can you hear me okay?

CHEN: Yes.

WISE: Okay. Let me see if you can see my overhead, maybe not. Can you guys see a page that's labeled "overview?"

CHEN: No. I think you'd better just explain your message, Bob.

WISE: Yeah. Let me just talk to you briefly. Okay. How's that? Okay. Good. So here's the picture. Briefly, from here we had the story of one striking patient, our index case. Her mother was concerned, contacted FDA, and as we listened we got the following story. At age ten months, she had uneventful vaccination against hepatitis B. Two months later, she developed the onset of hair loss about ten days after her second dose of hepatitis B vaccine. This problem progressed to complete baldness over the next three months. Her hair regrew over the following three months. Dose three of hepatitis B vaccine, together with oral polio at age eighteen months, we followed again. One week later, by complete baldness.

At this point, I think you know that the physicians considered the possibility of a vaccine role, but discounted it in the absence of any indication in medical literature or pathogen that this would be an expected event. This patient recovered her hair at about age 24 months. I should clarify she is not the patient you are looking at here. The one you're looking at here is patient two from the article. This index patient's hair is actually fairly long and healthy as of May 1997, our last follow-up. So the overview from VAERS is simply that we have an index patient; she had positive rechallenge. Positive rechallenge is a central feature in pharmaco epidemiology. It indicates that there's a greatly reduced likelihood of only a chance relationship between an adverse — an event and an adverse — an exposure and an adverse event.

We wanted the case findings. We found sixty total cases through early 1996; four of them had clear positive rechallenges. The signals, the hypothesis from VAERS is essentially dominated by hepatitis B vaccine. Forty-six of sixty cases had hepatitis B vaccine exposure and no other exposure in forty of those cases. Three of the clear positive rechallenges were associated with hepatitis B vaccine; one was not. One was a flu vaccine. Seventy percent of our patients were adults and 83 percent were female. The bottom line is that we've got a clear signal from safety surveillance indicating that vaccines probably can cause hair loss, but maybe only rarely. We have to interpret this information from VAERS and its predecessors in the context of the basic character of spontaneous report. VAERS and active surveillance like this have strength, including the open-ended character with the possibility of identification of previously unanticipated events. It's got a national scope so that even very rare events may come to attention.

Typically, therefore, VAERS was able to at least offer signals or hypotheses of safety-related possibilities, but these kinds of data certainly also have limitations, most notably under-ascertainment. So that one case observed may correspond to many incident cases that are not coming to attention. This is why we did not really know what the incidence rate for alopecia after vaccinations might be, and we still don't in adults, but these initial data from the Vaccine Safety Data Link are very reassuring. Spontaneous data do not provide denominators; they don't let us estimate incidence rates and generally do not allow consummation of hypotheses, but in this situation, we still have a very persuasive picture, particularly for hepatitis B vaccine. Vaccines have been absent from the traditional differential diagnosis for alopecia, but many reports here include four clear positive rechallenges. Biases could account for non-random distribution by vaccine, age and sex. So of course, we need continued systematic study to clarify the risk level for effects by age and sex. I'll be happy to take questions or wait for your discussion.

CHEN: Bob, one question was of your case series, was any of the hair loss permanent as far as you know? Bob, I'll repeat the question again. In your case series, was any of the hair loss permanent that you're aware of?

WISE: Well, you know, we haven't got follow-up for decades on these patients. I can tell you that just over half of those for whom we have follow-up did have recovery, but we have many cases in which we do not know for a fact that there was recovery.

MODLIN: Let me ask if there are other questions, maybe I can — maybe Bob Chen can relay them to FDA. Neal?

HALSEY: One thing that isn't spelled out very nicely in the manuscript is the distributions of the time interval after vaccination. You've addressed some of the problems with first, second and third dose on intervals, but it'd be very nice to see a figure, just a curve showing the time interval from vaccination to the onset with the first dose and then also with the second dose, and does it change. If there's a biologic mechanism involved as you have suggested, one would think that if it's the exact same mechanism that's occurring with the repeat challenges, that either the interval would be very close to the same or it might be shortened if it's an immunologic rule. I just don't see those data here. I wonder if you have them.

CHEN: Did you hear the whole question?

WISE: We have individual cases in which we have stories like a week after the first dose and then the same day, or within one day for a follow-up case. Patient two, for example — after follow-up, a subsequent dose — in

patient two at age five years, the patient received a dose of non-hepatitis B. MMR and TB time test followed within one day by loss of three regrown patches of scalp hair. In most of our cases, the data on the date of onset of hair loss is clear cut. I was able to read through all the cases and generalize that five of fifty provided some information about timing, had onset within one day; 84 percent within about one month, but the data from these cases are just not very complete, not very precise in many situations and that's, of course, because onset of hair loss is itself insidious in many cases.

MODLIN: Further questions? Geoff?

EVANS: This is for the VSD people. What would be the power of the study in order to detect something of rare frequency such as alopecia?

BLACK: We actually took both of them, but I can't remember what, you know, I can't remember that number. We started out with 500 and some cases, and then it depends on whether you include the cases with other attribution or not. The automated data, it turned out, was quite accurate. About 97 percent of the cases that were identified as alopecia from automated data actually were alopecia of some sort. I can't answer your answer.

EVANS: Well, I guess what I'm getting at is, I mean, it looks like the signal is real. I'm gratified, we're gratified that it doesn't look as though it's significant, but then how. . .

CHEN: Yeah. I think, yeah, we have that data. We just don't have it right in hand.

MODLIN: Further questions? Fernando?

BLACK: I think if your point being that given the number of exposed cases that we have, it would be desirable to expand the cohort to several years and we do plan on doing that. That's why this is preliminary, but it is what we have now.

MODLIN: Fernando.

GUERRA: Is the any information about race and ethnicity of the patients?

BLACK: We have that information, but have not analyzed it at this point.

MODLIN: Dr. Faggett.

FAGGETT: Were there any studies done relative to liver dysfunction, other effects of hepatitis B in those affected children? Also, Norplant in adolescent

patients is known to — has been said to cause alopecia. It's kind of interesting that the adolescent age group tends to be the most affected here. That's a two-part question.

BLACK: Some of the adolescents were on hormone therapy, birth control pills and other things, and those were amongst the group that were excluded from the primary analysis.

FAGGETT: And liver function tests?

BLACK: We did not identify anyone with abnormal liver function in any of the exposed cases.

FAGGETT: Okay.

CHEN: Bob Wise, are you aware of any of your case series being on either hormone therapy or birth control and/or abnormal liver functions?

WISE: I don't think any of our cases had hormone therapy or hormone — affected hormone variation such as menopause appearing to play a role, but I think you'll recall that there were about eight Illinois nurses in whom cosmetic hair straightening was attributed by a dermatologist as a competing cause, or in fact, he assumed that was the cause of their hair loss. So certainly, there are other factors that may play a role in some of the patients, but we don't specifically have hepatitis, or liver dysfunction or hormone therapy visible in the patient series that we have.

One other comment — you have to remember that hepatitis B, at least within our population, is given almost entirely to two groups; one is the newborn period. Newborns tend to go through a period of hair loss anyway, and I think even if some of this were occurring in the first few months of life, it might not be identified or might fit within the normal pattern. The other group is the adolescent. So that's another reason we're — but there are hardly any exposed cases in the intervening years.

MODLIN: Gina.

RABINOVICH: Just one comment that it's really valuable to have the VFC because I think the primary response when you hear about something like alopecia in children is that it's extremely rare, and that it has to be related. If nothing else, what this description of the differential diagnosis shows is there is — it happens with a certain background rate and there's a differential diagnosis that people need to think about in evaluating this. So it helps provide information which really doesn't exist systematically at a population-based level.

MODLIN: Good point. Are there other questions for either the people at the FDA, or Dr. Black or Dr. Chen? Bob, I should presume that you have some proposed language for us to discuss. So let's take the questions.

CLOVER: In the kids that developed alopecia, were there other — any other adverse events that were reported in these kids? Did they have a fever? Did they have any other responses to the vaccine?

BLACK: We reviewed the records and were not able to identify any other constellation of clinical symptoms associated with this.

CHEN: Thank you. As many of you know, Hal has been working on trying to get hepatitis B recommendations out. We thought that there was an opportunity if the Committee wished to add some language on this topic, and again, it is taking into account both the VAERS — the type of data that comes in through VAERS. Then the preliminary nature of the VSD data, we crafted some language, but you know, we'd leave it up to you as to whether you wished to add something. Again, I don't know how, when the next hepatitis B recommendations would come after this. We felt that this would give you a chance to get something in if you choose.

SNIDER: One thing that's critical, Bob, apparently for those that we know the outcome, it's been temporary hair loss. There's nothing in there that mentions whether this is permanent or temporary.

CHEN: Right. He said here the majority of the patients have recovered and we could strengthen that.

MARGOLIS: Bob, I'd like to make a comment because I think what's happened many times with the hepatitis B vaccine is this may just really raise the broader issue. I think it's an issue of this signal event. I mean, yeah, this made the newspaper in San Francisco and it brought a lot of attention. We have dealt with Guillain-Barré; we've dealt with optic neuritis; we've dealt with reports and abstracts of meetings of vaccine associated arthritis, all of which, I think, could be considered signal events and which if you look in VAERS, there are a fairly large number of cases in a case series. I guess I would just only raise to the Committee is how are you going to deal with signal events in terms of putting these statements into recommendations? Are you going to look at all — look for all signal events and then the data that goes with it? I think it really raises a larger issue than just alopecia in a particular setting.

MODLIN: Thanks, Hal.

SNIDER: I think that's a good point. I guess I need to go back to my point because it didn't get across. It says "the majority of patients have recovered." What I heard was that for all the patients in which you know the

outcomes, they have recovered. There's a difference between the data you've gave us and what this statement is.

GLODE: But the *JAMA* article says "four have persisted fault." That's what's in the medical literature.

SNIDER: Okay. So the information is wrong.

MODLIN: Alright. Neal.

HALSEY: I would discourage putting in any number of events because we well know from the VAERS data set and DTP, there are large numbers of events which we do not believe are causally related. So I think we should avoid numbers there. I think the unique thing about the VAERS report is that there are some cases of recurrence upon re-exposure, and that's not quite reflected in this language. So I think it should be a caveat that there's no proof of causality here, but that's what I would put in. I don't know that we want to try to write the exact words in a large committee like this, but I think that's what belongs there.

MODLIN: I think the question that the Committee needs to deal with is whether we want any reference to any statement whatsoever. I guess what I'd like to do maybe is to discuss specifically that issue and get a sense of what the other members of the Committee feel. We'll go around — Dave and then Marie.

FLEMING: That is the issue that I wanted to raise as well. I guess for people that have been around longer, I have a question about protocol and consistency. When there are and have in the past been reports of where potentially not life threatening complications from vaccination, has it been traditionally the ACIP's role to make the first determination or are there existing channels that we need to honor for evaluating evidence related to vaccine adverse events? Does the FDA have a process that they're going to go through to evaluate this evidence and come up with a statement package insert change? Are we getting at odds with the existing channels for evaluating adverse events? That's one question I had. The second is the consistency question that Hal brought up. If we do choose to take this issue on — an estimate by folks who know — how many other issues are there out there like this for even this vaccine or others that we would be obligated to take on as well for consistency's sake?

MODLIN: I'm not aware of any standard procedure for dealing with each individual adverse event. John, you may want to address the issue.

CHEN: Maybe address the second question since I've been at this event for over the last few years. I think the thing that is unusual about this, I think as

Hal pointed out, there are many elevations in which there are multiple other etiologies possible, but there's no unique clinical, unique laboratory findings, in which case then we don't really touch it until we have some type of epi data to put it on the table. I think this one does stand out as being different. I think this one, the unique clinical syndrome of the positive rechallenge is very hard to refute. I think can someone out there who challenges that "give me a plausible alternative scientific explanation for those cases." If so, then we need to hear that and think about that, but if not, then I think it does put it a little different than the other ones that — and sure there are, you know, thousands of those in VAERS.

MODLIN: Dave, did you have your question answered?

FLEMING: Not the first one.

MODLIN: Okay.

LIVENGOOD: I don't think there's really a set process. I mean, certainly for table injuries if you're talking about the National Vaccine Injury Compensation Program, that is a long administrative process that I don't think we're anywhere near close to beginning to look at.

FLEMING: The vaccine safety issue, I mean, because this is something that needs to be evaluated by the people who look at vaccine safety, and decide whether or not the vaccine should be licensed and what the package insert should say about side effects. I mean, I don't know.

LIVENGOOD: I don't think that there's been any clear. . .

CHEN: Well, Bob Wise and Jerry Donolan may want to comment on what the current process at the FDA in terms of adding this to the package insert.

WISE: Can you hear me okay?

CHEN: Yes.

WISE: One of the two hepatitis B brands licensed in the United States had alopecia added to the adverse events also observed after marketing began — just the word added — I think it was about 1995. Appropriate labeling consideration is still under consideration for the other brands. If one of the manufacturer representatives wants to say something further, they can, but these are proprietary documents until they are actually issued. So we can't say anything until it becomes public information.

MODLIN: Marie, you were next.

GRIFFIN: I think there are a lot of things in the package insert that follow, may follow a drug or a vaccine that does not imply a causal relationship. So I don't think the package insert is very informative about causality. I think we're really obligated to make that determination if people are trying to weigh the benefits and risk. So I think safety is in that sphere. In this case, I would agree with Bob with the challenge/rechallenge. The article published in *JAMA* is very provocative. I think it's convinced a lot of people, so in that light, I think these data from VSD are very reassuring. So I would be strongly in favor of including it.

SNIDER: I think on that issue, it seems to me though that we have established in our epidemiology textbooks a number of items that we use to establish causality. The one that Bob is pointing out is a very important one in that you have to have the exposure before you have a health outcome rather than the other way around, but one needs to ask the other questions too because I'm not aware that one makes decisions about causality based on just one of the criteria.

GRIFFIN: Well, I think that's why the data from VSD is addressing, not only the temporal issues, but the strength of the association and the consistency, et cetera. So I think that is an epidemiologic study that really does address all those causality issues.

LIVENGOOD: I'd just like also to point out that, I mean, I know Marie, and Bob and I in years past did a lot of time working with pharmaco epidemiologists where this is a basic principle in some ways of pharmaco epidemiology when you get, you know, you challenge somebody with it; they have the effect, you know; you stop the drug; they don't have it; you rechallenge them; they get it again. I mean, most pharmaco epidemiologists would buy that as a causal argument, as close as you can get almost to a control trial. So I think for us to fall back on how we evaluate observational evidence for a link for causality, I think it's just not quite — I mean, maybe that's why some of us feel that the Wise article made it a fairly strong causality argument in the first paragraph of the discussion that "the features of this are strongly supportive of a causal association." When you get into our other data, what we're saying is that if there is a causal association in some people, it's very rare. It's a small effect on the population basis; it's not significant. That's where we run into our other arguments and that's why I sort of favor adding something, but then providing the data to say if it does happen, it's rare. It seems to be almost a characteristic of the person rather than of the exposure in some ways.

MODLIN: Thanks, John. Geoff?

EVANS: To me, this became a vaccine safety issue with the *JAMA* article and its title, *Hepatitis B After Childhood Immunizations*. Given that, it seems to me that we are obligated to provide some clarity on this. There are

signals in VAERS and there are signals. The rechallenge data to me has always been a striking unique aspect to this issue. If this is also, as Gina was saying, this is a vaccine safety win/win because we have the signal provided; it was publicized. Now we have more active data that's been presented and I think puts it in perspective, and at least says to us that if it is real, it's something that's not occurring in any frequency that should cause us great concern. So I think that all these things point to that we should put some language and clarity on it.

MODLIN: Chinh.

LE: Yeah. I would agree with it, you know. If it was penicillin, there's absolutely no question that this is, you know, the label being in the chart that says "allergic patients never receive it again," you know. The fact that this study is "reassuring," I still think that Geoff's point in terms of the sample size, the type II error is not quite answered because if the estimate is eight cases per 100,000 doses and so on, and this study looked at eighty-some doses — a very courageous, you know, review of several hundred charts in three months — that's very good, but you haven't entirely answered the question of the frequency of this. So I'd really formally support that this needs to be brought to the public in some way rather than just kind of shoving it under the rug.

CHEN: Let me just comment on that real quick. We did an automated look and then because we — since this is a new outcome we never studied before, we decided to go to the gold standard and go to the chart. Now that we have done the chart, we found out that in fact the automated data is quite good on alopecia so that we in fact have much larger automated data available to put the work on this. So one option is that in fact we might be able to come up with, you know, much nicer data if we both feel comfortable that, you know, with the 97 percent accuracy that we found on the initial chart review. So that's one option.

MODLIN: Thanks, Bob. Neal?

HALSEY: In many ACIP statements, there is information provided that does not necessarily say it's a causal event. Oftentimes, especially when we were struggling for many years with DTP associated adverse events, information was provided; the data that were available summarized very concisely so that it was clear that the ACIP was aware of the issue. If you don't address the issue in the statement, then people will say you're either ignorant or you're trying to hide something. So I think it can be done without making a determination of causality. That's probably beyond this discussion right now. I mean, it's suggestive, but it's not conclusive and I would strongly be in favor of putting in some wording to address the fact that it might occur.

SNIDER: Well, I don't — just responding to that — I don't think it's necessary. It guess what I was trying to get at is that in terms of making an absolute determination of causality, I personally would not feel comfortable approving something that didn't meet more than, you know, one of the criteria. On the other hand, as far as making a decision to put something in or not put something in, it seems to me that if it does meet one or more of the criteria for causality, then you can start making an argument for putting the information in — not that you have necessarily made the complete case for causality.

I was just suggesting that that might be one way to look at these things to respond to the issue that Hal raised because there are a lot of claims that people can make. One way of looking at those claims might be to look at the criteria for causality and ask the question "Does it meet any of these criteria?" Because if it fails all the criteria of a cause and effect relationship, then one might choose to not deal with those allegations, Hal, and in other cases like this in which at least one of the criteria is fulfilled, make a decision to include it in a statement. Because I mean, people have said, you know, do we have any — I don't think we have any past policies for doing this. So what I was trying to do is contribute to some discussion on how we might, not just deal with this issue, but the broader issue of which allegations do we put in statements? Which possibilities do we put in statements and which not?

MODLIN: A couple more comments. Yes?

MAST: Eric Mast. I was wondering whether it's been considered whether this could be a phenomenon related to injections and not related to vaccines themselves? Is it all part of the vaccinations?

CHEN: Bob Wise has probably looked at this most closely in terms of other causes of hair loss. The question was could just the injection alone rather than the product vaccine cause it? I guess right off-hand, I would argue that's probably not the case because if that's the case, then we would see a fairly random distribution of this phenomena after all the other vaccine products and all the other injections that are given, but Bob, you may want to add to that.

WISE: Well, remembering two or three things: first, that the pattern of vaccine association — the frequencies by vaccine in the VAERS report — could be due to biases. We're particularly suspicious or concerned about the possibility that health care workers might be much more familiar with VAERS reporting, the target groups for hepatitis B vaccination. So that alone could account for a lot of the concentration on hepatitis B in VAERS. Second, I want to emphasize that we've got about a fourth of the sixty reports — these being patients who did not have exposure to hepatitis B. So certainly, our signal from VAERS is dominated by

hepatitis B, but it is not limited to hepatitis B. In fact, I think I alluded a few minutes ago to the update on patient two from the *JAMA* article. At age five years, this patient who previously had lost hair twice after hepatitis B injections now received MMR and TB time tests. This was her third TB time test and I think her second MMR. This was followed within one day by loss of three regrown patches of hair.

So the possibility that this is a less specific response — immunologic response to stimuli rather than a very specific response to the hepatitis B antigen — has to be considered at least in some patients. Recall that at least, I think it's something like half of alopecia cases do not have an identifiable ideology. So the possibility that a wide variety of immunologic stimuli might be capable of provoking cross-reacting auto antibodies, or modulating antibodies or some mechanism leading to hair loss, I think, does warrant consideration. I think it would be premature to say that hepatitis B vaccine is clearly the only cause of concern.

MODLIN: Yeah. One final comment and then we need to bring this to closure. Sam?

KATZ: Thank you, John. I hate to pre-empt the last comment, but following along with what this gentleman said, I think it's very important that we differentiate, you know, causality from association. I'm quite convinced when you see unusual responses of this sort, he used the term "autoimmune" and that's a good one. I think that as our geneticists using single nucleotide polymorphisms or other technology are able to differentiate what may be quite different in the immune response of individual A who's one in a million or one in two million in a population. These things will fall out as being due not primarily to the antigens themselves, but to some degree of unusual immunologic response in the host recipient.

MODLIN: Thank you. If you think the Committee does need to consider — and call the question here. I guess probably the first thing we need to address is do we want to make a statement here? Then I'd rather not get bogged down in the individual wording although there — I think that if we do decide that a statement is preferable that we can make some suggestions, some general suggestions and not get — not worry too much about what the final paragraph is going to look like. Let me ask for a vote of the voting members who would prefer to have a statement along the lines or similar to that proposed by Dr. Chinh. Could I see a show of hands? I'm sorry?

CLOVER: Is further education a conflict of interest or not?

MODLIN: I would judge that this is a rather — well, Dixie? This involves two vaccine manufacturers. I don't believe that — I think that this is an issue that is so

peripheral that I don't believe that anyone should be conflicted on this particular issue. Does anyone disagree with that judgment? Okay. Dixie pointed out Kevin's out here.

FLEMING: I just have a point of clarification about the vote.

MODLIN: Yes, Dave.

FLEMING: You've prefaced it as it was going to be a two-part: one, should there be a statement and then second, discussing the content.

MODLIN: Right.

FLEMING: But the motion you put forward was a statement, so then I'm confused what we're doing now.

MODLIN: I'd be welcome to entertain a motion from the other members of the Committee. So any further discussion from the voting members about this? Okay. Those in favor of including a statement on the hepatitis B, raise their hands. It appears to be that it's unanimous amongst the eight voting members that are present.

SNIDER: Dr. DeBuono. . .

MODLIN: Dr. DeBuono is absent.

SNIDER: . . .is absent.

MODLIN: And Dr. Sherrod is absent.

SNIDER: Right. This is for the record for the transcript.

MODLIN: Okay. Let's take five more minutes and if there are specific suggestions regarding the content of the statement — yes, Chuck.

HELMS: Causality is not included as part of the statement.

MODLIN: Can you speak into the microphone, Chuck?

HELMS: I move that this statement not imply causality.

MODLIN: Okay. It's been moved and seconded that the proposed statement not imply causality.

GRIFFIN: You think this does imply causality?

HELMS: No.

MODLIN: Okay. Alright. Any discussion? Those in favor? Yes, Fernando.

GUERRA: For clarification, is there a need to have any sort of time sequence in there that the first sentence — "with sudden hair loss after vaccination on more than one occasion" — should there be a temporal relationship of so many days? I think that they reported that generally this was within a sixty-day period of time.

MODLIN: How do others feel about Fernando's suggestion; that there is the inclusion of some time interval with respect to some incubation period, so to speak, between immunization and the occurrence of alopecia? Bob?

SNIDER: That's a separate question.

MODLIN: It is a separate question. That's a good point. Let's deal with the motion right now, which is the statement not include any suggestion of causality. Those in favor of the motion? The vote is the same as before — eight members present, Dr. Sherrod and Dr. DeBuono absent.

CHEN: Can someone help me kind of — if you read this current language, I don't read causality in there. If you feel that it does, then let me know.

LIVENGOOD: I don't think it was a criticism of the language; it's guidance.

CHEN: No, no, no; I know. I just wanted to know for legal advisors.

HELMS: I don't believe that Dr. Helms indicated that he's detected any in the statement either; just that we're crafting the statement. In the interest of time, I would suggest that unless there are major issues regarding the proposed language that we move on and that if there — for minor issues that you could certainly submit them either directly after the meeting.

SNIDER: The one thing that might be helpful to people on that issue would be to understand what happens, and this is to be incorporated in the hepatitis B statement which will have to come before the Committee again. So for those who have particular concerns, it seems to me — well, Bob, am I correct that they, people will see this again; Committee members will see this again?

CHEN: Well, I don't know where Hal went. I don't know exactly where the recommendation is in the process. I know he's been waiting for a long time. What I'd like to do is to be helpful so that we'll work with the Committee just to get timely acceptable language that he can meet his publication deadline.

SNIDER: Well, all I was saying that this is not their last shot at it.

MODLIN: Chinh.

LE: John, can I just make one suggestion, please? This topic is so interesting to the public. The discussion here seems so valuable that what I'd like to suggest is to have this preliminary report written up in the MMWR so that the reference in the final ACIP recommendation doesn't say "personal communication." Because I — when I read things like "data in file" and "personal communication," it just blows my mind. I think it's better to just have it as a short article in the MMWR, then people can refer to it.

MODLIN: You're going to be checking on your part for the staff? Terrific. Thank you. Let's move on to the next topic. Bob, thank you very much, very interesting presentation. Dr. Wise and others at the FDA, thank you for your participation. The final item on the agenda is informational issue only and that has to do with the supply of immunoglobulin. I assume that that means the suppl of IVIG. Dr. Yusef will be presenting. Pardon? HBIG, I beg your pardon. I thought it was IVIG. I understand there's a marked shortage, but this is — okay. Go ahead.

YUSEF: Turn down the lights, please. Good afternoon. This informational presentation is regarding the use of hepatitis B immune globulin for the prevention of hepatitis B virus infections, and whether there is a potential shortage or a potential for shortage of HBIG supply currently. This is for information only and no actions are being proposed for the ACIP at this time. As you all know, it's estimated that approximately 100,000 to 140,000 persons are infected each year in the United States with HBV, and that between 5,000 to 6,000 persons die due to HBV-related conditions. HBV is transmitted by sexual contact with infected persons, exposure such as injection drug use and occupational exposure, and the transmission from an infected mother to her infant. Infants infected at birth are much more likely to acquire chronic HBV infections than are adults.

One of the major uses of hepatitis immune globulin or HBIG is in the prevention of prenatal transmission of hepatitis B virus. Each year, approximately 20,000 HBSAg-positive women give birth in the United States taking into account the prevalence of HBe antigen-positivity among these women. To an HBSAg-positive person, it is also indicated for liver transplant patients. The recommended dose of HBIG for infants born to HBSAg-positive mothers is .5ml, and in all other situations, .06ml for a program of body weight. Manufacturers' formulations in which HBIG has been available include .5ml syringes, 1ml vials and 5ml vials.

The CDC began contracting for the purchase of HBIG for the states in 1990. Between 1990 and 1992, HBIG was purchased from Abbott

Pharmaceuticals. From 1993 to 1996, CDC contracted with North America Biologics or NABI, which had purchased Abbott's license. Although Abbott still produced HBIG, NABI held the license and the product from NABI was named HBIG. The last contract between the CDC and NABI expired in August of 1996 and no new contract could be agreed upon. Since then, HBIG had been purchased using the Veteran's Administration's federal supply schedule. On December 31st of 1997, this contract also expired and currently there is no contract in effect through which the federal government can purchase HBIG.

This slide presents the quantity of HBIG purchased by the states using CDC contracts and sources of funds used since 1993. Last year, approximately 14,600 milliliters of HBIG were purchased by the states through the federal supply schedule using VFC 317 as well as state funds. There has been some concern recently regarding the prospect of a shortage of HBIG. The context for this is that Abbott Pharmaceuticals is no longer producing HBIG for NABI. NABI has contracted with a new Canadian-based manufacturer named Cangene to produce HBIG. However, NABI will be able to supply the Cangene-produced HBIG only after it receives an FDA license. NABI plans to submit their request for approval in the summer of this year and in the normal course, an approval can be expected twelve to eighteen months after that.

NABI currently has 25,000 5ml vials of HBIG in stock and these vials are labeled as single use. NABI has indicated that under the circumstances, it does not plan to enter into a contract to sell any of this present inventory to the CDC. To our knowledge, the only other manufacturer of HBIG in the United States is Bayer Pharmaceuticals. Bayer's product is named BayHepB. Bayer currently has a limited stock of HBIG, but does expect new lots to be released some time in February. However, their plant production schedule does fluctuate, and therefore, they do not plan to venture into a contract for selling HBIG to the CDC at the present time. We recently carried out a survey among states to assess their practices with respect to supplying HBIG to providers and institutions, and their anticipated needs for 1998. Forty-one states responded to our survey; 33 of these states indicated that they provided HBIG directly or through local health departments to health care providers and institutions.

In 1997, 24 states provided HBIG for administration to infants born to HBSAg-positive mothers and ten states provided HBIG for administration to adults and adolescents. Eight states indicated that they did not provide HBIG. The 33 states in our survey who provide HBIG indicated that they currently have 47 .5ml HBIG syringes in stock, but anticipate a need for approximately 4,000 such syringes in 1998. The current inventory of 1ml and 5ml preparations among these states is 0 and 800 vials, respectively, and that their 1998 needs are approximately 1,900 and 5,300 vials respectively. As can be seen, states currently do not have an inventory of

HBIG to meet their needs for 1998. This slide presents a distribution of states with respect to current inventory and 1998 needs for HBIG. Seven states in the survey indicated that they have no HBIG in stock and these states do anticipate a need for approximately 4,000 doses in this year.

The inventory of eleven other states is less than half of their anticipated need for 1998. All of the states in our survey who provide HBIG purchased HBIG last year using the federal supply schedule, and no other mechanism such as purchasing directly from a pharmaceutical manufacturer was used. With respect to a potential for an absolute shortage of HBIG, based on information provided to us by the two manufacturers, we estimate that the current inventory of HBIG among these manufacturers and pharmaceutical wholesalers is sufficient to meet the overall demand for HBIG in the United States for at least four months. After this period, the possibility of a shortage will depend on several factors. These include production and release of new lots of HBIG by Bayer; how long it takes for an application and approval of the NABI/Cangene-produced HBIG; and whether or not the current inventory of 5ml preparation can be used to draw multiple doses. It should be noted that the likelihood of a shortage of HBIG is low. Bayer has already indicated that they expect new lots of HBIG to be released some time this month.

Although an HBIG shortage is unlikely, we still have tried to roughly qualify the potential impact of such a shortage. It's estimated, as I mentioned, that 6,000 to 9,000 infants would become infected prenatally with HBV if no immunoprophylaxis were used. Timely administration of HBIG and hepatitis B vaccine have been shown to be 80 to 98 percent effective in preventing prenatal infections. Administration of that vaccine alone without HBIG has been shown this to be 70 to 95 percent effective. Therefore, without HBIG, there may be a possibility for additional prenatal HBIG infection. Failure to use HBIG may also result in additional infections among individuals exposed occupationally or sexually to HBV.

To address the current situation where there is a relative inadequacy of HBIG supply in some states, and to ensure that an absolute shortage does not occur, actions we're considering including expediting FDA approval process for the new NABI/Cangene-produced HBIG. This will enable NABI to adequately meet the potential demand for HBIG. In the interim, we may explore the possibility of using NABI's current inventory of 5ml single use label vials for multi-dose administration. According to NABI's HBIG product manager, these 5ml vials contain thimerosal preservatives and are the exact same products that were used as multi-dose vials in previous years. For some reason, there has been a change in labeling for NABI and we are currently following up with the VA regarding this matter.

With respect to enabling states to purchase HBIG to meet their current needs, we can explore the possibility of entering into a small contract with NABI with regard to their current inventory. NABI has indicated that if their currently stocked 5ml vials were approved for multi-dose use, they would be interested to enter into a small contract possibly for 5,000 5ml vials with the CDC. Additionally as a long-term solution, we need to secure a long-term contract with the manufacturer. As states have indicated, the use of 5ml vials for infant administration often leads to wastage because after one or two doses are withdrawn, the rest of the vial may be discarded. A new contract should be for .5ml preparation. Other options for consideration include that the federal government stops purchasing HBIG for the states, and leaving it to the state to purchase the product therapy according to their needs. The CDC currently does not purchase any other immunoglobulin products for the states. Additionally, states may also choose not to supply HBIG. Administration of HBIG occurs at hospital and provider level. The responsibility for acquiring HBIG can remain at this level with cost being picked up by third party pairs. Our survey showed that a number of states currently do not provide HBIG.

Finally, future consideration is whether administration of hepatitis B vaccine alone can be considered equally effective as a combination of the vaccine and HBIG in preventing infection. There's only state, Alaska, does not carry out HBSAg screening on pregnant women, and therefore, does not administer HBIG to infants of HBSAg-positive mothers. An active strategy instead has been to vaccinate all infants at birth with hepatitis B vaccines. Although the prevention efficacy of the vaccine alone has been shown to be very similar to that of HBIG and vaccine combinations, further examination of currently available data and possibly the gathering of new data is necessary before such recommendations can be appropriately considered. Along this line, we can also consider prioritizing the use of HBIG if infants or mothers who are HBSAg-positive and HBe-antigen positive are much more likely to become infected than infants or mothers who are HBSAg-positive, but e-antigen negative. Therefore, administration of only the vaccine may be sufficient for the latter group, and the combination of HBIG and hepatitis B vaccine can be administered to infants born to mothers who are both surface and e-antigen positive. However, this would require e-antigen testing of HBSAg-positive mothers and the feasibility of this is unknown.

In conclusion, it's unlikely that there will be a shortage of HBIG. However, the supply of HBIG in some states is inadequate relative to the quantity they anticipate they need to supply in 1998. Currently, there is no contract in effect through which the CDC can purchase HBIG for the states. Possible actions include seeking an expedited approval for the new NABI/Cangene-produced HBIG; securing a limited contract with the purchase of NABI's currently stocked 5ml wild to see if they can be used

for multi-dose administration; and securing a long-term contract with the manufacturer for the purchase of HBIG. I'll end there. Thank you.

MODLIN: Any comments or questions for Dr. Yusef?

SPEAKER UNIDENTIFIED: Hussain, I spoke with the product manager of NABI this morning and Abbott has done a historical search of documents. They have sufficient proof on hand that the bacteriostatic nature of the thimerosal will warrant multi-dose use. Abbott has indicated that they will be seeking a revision of the labeling today from FDA — and however long that takes to process — and asked that CDC send a letter in support of that particular action.

MODLIN: Thank you. Carolyn, any comments?

HARDEGREE: No. I think that if data is available, I think it will also depend upon what the situation is about whether this is final label material that's been distributed. So those issues, I will address with Dr. Epstein when I get home.

MODLIN: Any other — yes, Fernando.

GUERRA: Just a comment not necessarily directly related to the HBIG discussion, but I think this certainly serves as a sentinel discussion for what is perhaps an even more relevant public health concern, and that is the general shortage of the immune globulin products that, you know, for a considerable period of time now, we have had great difficulty in maintaining a constant supply of immune globulin for just post-exposure prophylaxis in the instance of hepatitis A. It has certainly been a problem with rabies immune globulin and a number of the other — and I think as there is, or it seems to be an increase in demand for some of these biological products, there is potentially a very serious threat to or ability to respond to community type of outbreaks. I just wonder if maybe for our June meeting it might be important to consider placing on the agenda something that would give us a better idea of what the supply and demand curve has been for immune globulin products overall, and to see if we could maybe begin to frame some recommendations more specifically beyond just the HBIG discussion.

MODLIN: I'd have to ask Dixie if there's anyone at the CDC who actually monitors or has access to that information?

SNIDER: I mean Alex and others might be able to answer than I, but I don't think we have that kind of, you know, that kind of information. We have some anecdotal information, but as far as absolute numbers of, you know, as far as supply and demand, I'm not aware of it.

LIVENGOOD: No. This is — we just know about this one primarily because we supply it. When we lost the contract — when no contract, when no one bid on the contract — excuse me — and then we, our information about their total use is we call the manufacturers. "How much of it did you sell that last year? Would you tell us, please?" They did so we have information, but it's not something that we know much of. I was just talking — I don't know that we at CDC monitor much about other immunoglobulin supplies.

MODLIN: Well, it's in short supply. I was unaware of that.

GUERRA: Well, I think that, you know, we've certainly had to ration it. We've had to go through a fairly rigorous decision-making process in the instance of post-exposure because at least at the state level, there is a shortage. It all seems to be, at least the explanation is, that the manufacturers of these products, for a number of reasons, are not producing the same volume that they did at one time. I think one of the major producers of immune globulin products actually had shut down their facility for some period of time. So I think it, you know, it does translate into some important public health considerations. I'm just glad that whether it was related to HBIG, I think it opens up the broader discussion.

SNIDER: There are a number of factors. We could potentially have some discussions. We'd have to talk to the folks at FDA. We could potentially have some discussions around some of the factors that have caused some of the problems, but it gets into hepatitis C testing. I mean, there are a number of issues that have led to problems with regard to supply. All I was indicating though, I think as far as being able to match up supply and demand, we have only anecdotal information — not numbers that we could supply.

MAWLE: We're aware of the problems. We don't have actual numbers; no, but we're not monitoring it. Certainly with respect to rabies vaccines, we have several ongoing programs looking for substitutes for rabies immunoglobulin because of the problems. It certainly would be possible to provide that kind of information.

FLEMING: I think it would be potentially useful maybe to have at least an informational update by the folks in the hepatitis branch. They are actively involved in rationing Ig supplies to states. We have to get approval from CDC for getting Ig at the state level for large outbreaks. I think Hal has some interesting information about use of Ig, and particularly, off-label use contributing to at least some of the problem with the shortage right now.

MAWLE: That's true. They can certainly do that.

MODLIN: Rich.

CLOVER: The corollary to that is — is there any other information with regard to using hepatitis B vaccine for post-exposure by itself, as well as hepatitis A vaccine by itself? It seems some of that data would show. . .

MODLIN: With newborns, there's no question about that. I think it's a matter of pulling that together. As Dr. Yusef just mentioned, taking a closer look at it than perhaps any of us have in the past. Obviously, this is an issue that's much broader. It's not just an issue for CDC or even for the entire public health service. It's even a broader issue than that, so I think there's no question. . .

SNIDER: I think what we'd like to do is discuss it within CDC and with our partners at FDA about what kind of presentation we could put together for the next meeting that might be useful for the Committee.

MODLIN: The last item on the agenda is — I'm sorry, yes.

GRAYDON: I would encourage that to be pretty broad. This has come to us in the context of prophylaxis for people with pediatric AIDS — children with pediatric AIDS. Apparently, there's a tremendous shortage allegedly in the IVIG area. We've been requested oddly enough, Dixie, that CDC needs to issue a statement to hospitals that there is a shortage. I hear you saying you don't know whether there is or not, but it's become a very serious issue.

MODLIN: For IVIG. . .

GRAYDON: Right.

MODLIN: . . .rather than for specific immune globulins. I think all of us who work in — or clinicians are very acutely aware, as well as the public health people are of the shortage of IVIG. I suspect it's multi-factorial. There's no question that it is used for many clinical indications for which there are not necessarily sufficient data to indicate that it's a good use of IVIG. I'm sure that increased usage contributed to the shortage and I expect that there are other causes as well. Maybe if we are including that on the agenda for next time, we could include regular IVIG. I'd rather not comment on the use of IVIG with children who have pediatric HIV infection, at least not publicly. Alright. Other comments on this?

The last item on the agenda is that we do have a period for public comment. To my knowledge, no one has signed up to make a public comment on any issue that has come before the Committee so far. Sam, now's your chance.

KATZ: Now's my chance. I'd like to make a public comment. With the Chairman's permission and your indulgence, I'd just like to make a historical note, which is in the early 1980s, Dr. Kathryn Wilford, Professor of Pediatrics and Virology at Duke University chaired this Committee. Subsequently, Dr. Samuel Katz, Chairman of Pediatrics at Duke chaired this Committee. He was followed by Dr. Jeff Davis, Resident and Infectious Disease Fellow at Duke University. Now he's followed by Dr. John Modlin, who was a medical student and an intern at Duke University. Now we haven't been able to endow the Chair financially, but we're very pleased and very proud to have endowed it intellectually.

MODLIN: You can bring a flag to the next meeting and we'll put it — thank you all very much. It's been a terrific meeting. I look forward to seeing you in June.

[*THE ACIP MEETING ADJOURNED ON FEBRUARY 12, 1998 AT 1:20 P.M.*]